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THE INCIDENCE OF "PSYCHOGENIC" FEVER IN A UNIVERSITY HOSPITAL

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INTRODUCTION

BEESON,[1] Breen,[2] and Keefer[3] describe a transient elevation of temperature occurring immediately following hospitalization in patients without apparent reasons for fever. Alvarez[4] and Friedman[5] observed patients with transient elevations in temperature during their first clinic visits. Many cases of transient fever associated with emotional and mental processes, or "psychogenic" fever, have been reported in the literature. Studies of the incidence of this phenomenon have been limited to (1) the incidence among 324 draftees during physical examination,[6] (2) the incidence among a small series of psychoneurotic patients during their first clinic visits,[5] and (3) the incidence among a small series of patients ". . . suffering from functional cardiovascular disease."[7] No study has been found in the literature of the incidence of this phenomenon among patients admitted to a general hospital. The present study was designed to determine the incidence of psychogenic fever in a university hospital population. Such information might be of diagnostic and prognostic value.

REVIEW OF THE LITERATURE

Wynn[6] reported that 67 per cent of 324 men being examined for the draft had a temperature above 99° F., with 15 per cent having temperatures over 100° F. He also noted that the average temperature of 40 nurses recorded just prior to

their taking state board examinations was 98.9° F. as contrasted to the average temperature of 98.3° F. after completion of the examination.

Falcon-Lesses and Proger[8] reported a well-documented case in which the diagnosis was made not only by the exclusion of organic disease but also by the experimental production of fever with emotional stimuli. They demonstrated an increase in temperature which was associated with the patient's visits to the clinic, with venipuncture, with pelvic examination, with the entrance into her hospital room of two physicians, and with the suggestion that she needed an operation.

Beeson[1] noted that it is not unusual to find a number of slight elevations in a pediatric ward immediately after the visiting hour. Friedman[5,7] reports ". . . that approximately 30% of patients suffering from functional cardiovascular disease exhibited neurogenic hyperthermia." He defined "neurogenic hyperthermia" as a low grade fever of 99.0 to 100.4° F. associated with psychic or emotional stress. He also noted that 18, or 45 per cent, of 40 psychoneurotic patients with "somatic references" exhibited fever of 99.2 to 99.8° F. during their first visits to his office. He referred to those patients with a ". . . neurosis with peripheral vascular components." As a control, he studied the temperatures of 100 other patients ". . . who were neither psychoneurotic nor suffering from an infectious disease" under the same circumstances and found only one who showed a rise in temperature (99.0° F.). He also noted that the average temperature of three "psychoneurotic" patients engaged in an exciting card game rose 1.5° F. during the first hour of the game; whereas two "normal" subjects involved in the same game showed rises of only 0.1° F. and 0.2° F., respectively. "When the same game was repeated with all elements of gambling removed, no significant rise in temperature occurred in any of the hyperthermic patients—clearly indicating that it was not the physical activity of card playing itself which had provoked the fever previously observed."[5]

Kintner and Rowntree[9] reviewed 100 cases of low grade, long-continued, idiopathic fever and found (1) that the oral temperatures varied from 99 to 103° F., (2) that 66 2/3 per cent occurred between the ages of 20 and 40, whereas only 38 per cent of their clinic patients fell within these ages, (3) that females constituted 72 per cent of the group with fever, whereas only 54 per cent of clinic patients were women, and (4) that associated symptoms were primarily exhaustion, nervousness, and loss of weight. They regarded 25 of these patients as neurotic.

Reimann[10] studied 16 women whose oral temperatures had reached levels slightly higher than 98.6° F. over a period of years. Five of these women were apparently normal and healthy; 11 more were regarded as neurotic. Reimann concluded from these studies ". . . that a certain proportion of normal individuals have temperatures regulated at levels slightly higher than 37° C. (98.6° F.) and that temperatures at these levels are often found in neurotic persons."[10]

Smith[11] reviewed 51 patients with fever of undetermined etiology, of whom 22 had had low grade fevers under 100° F. for periods of 13 months to almost 4 years. No organic disease was found in this group of 22, and the chief symptoms were ease of fatigue, chest pain, weakness, "effort syndrome," and emotional lability.

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METHOD

The population studied consisted of all patients admitted for the first time to the North Carolina Memorial Hospital in 1956. The first admission was considered to represent a reasonably uniform and potentially "stressful" situation for most patients since it involved an abrupt change from their customary environment to a new one which was usually strange and frequently threatening. It is recognized that some patients may have been in other hospitals previously and that this may not have been the first hospital experience for all patients. If such previous hospitalizations decreased apprehension about admission to the North Carolina Memorial Hospital and any associated "stress," they would tend to reduce the incidence of "psychogenic fever" rather than increase it. To nullify the effects of different environmental temperatures, the months of the entire calendar year were sampled equally. The sample studied consisted of alternate first admissions, excluding newborn infants, during 1956.

Figures for first admissions to the North Carolina Memorial Hospital by services are not kept. To determine this distribution, a random sample equal to 5 per cent of all first admissions was taken. In accordance with numbers selected from a table of random numbers, the chart of every sixth, thirty-third, and fifty-third patient admitted each day was examined, and when a first admission occurred, the admitting service was recorded. The estimated distribution of all first admissions among services as determined by this sampling method is given in Table I.

TABLE I. DISTRIBUTION BY SERVICES OF FIRST ADMISSIONS TO NORTH CAROLINA MEMORIAL HOSPITAL, DURING 1956, AS DETERMINED BY A 5 PER CENT RANDOM SAMPLE

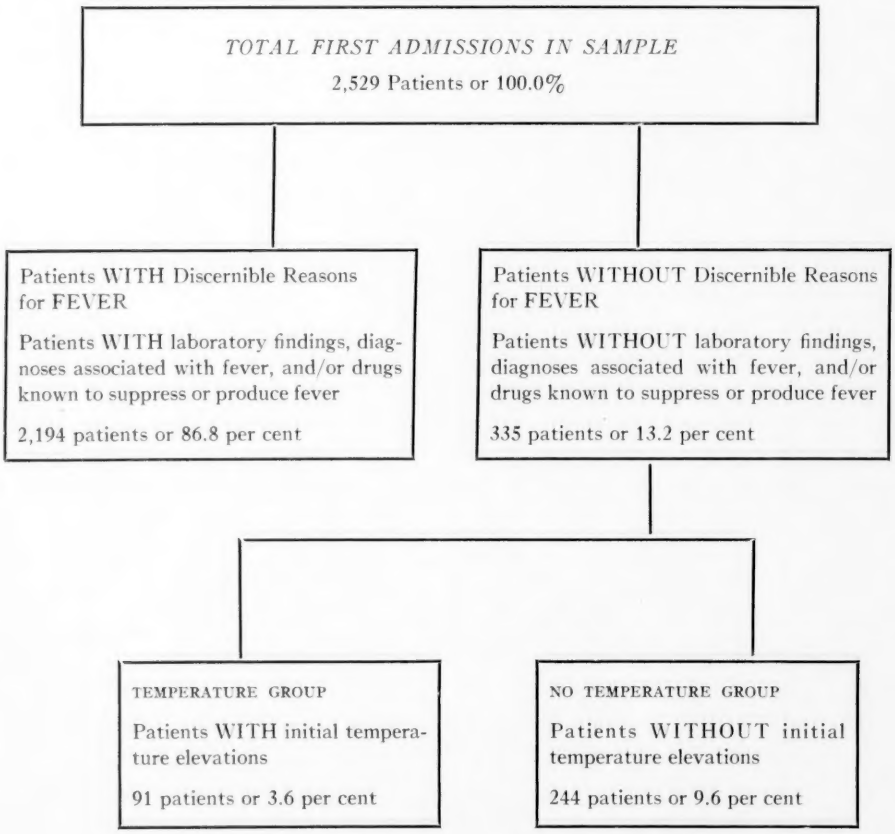
	NUMBER	PER CENT
Psychiatry	248	9.8
Medicine	941	37.2
Surgery	910	36.0
Pediatrics	215	8.5
Obstetrics	215	8.5
	2529*	100.0

*Actual number of first admissions in original sample.

In this study the existence of "psychogenic fever" as a psychophysiologic entity is accepted. Rigid criteria were used to exclude other causes of fever, thus leaving a residue of patients who have an unexplained initial temperature elevation which subsides spontaneously. It is this group which is believed to represent "psychogenic fever." All patients in the first admission sample who had a diagnosis, laboratory finding, or drug that might be associated with an elevation of body temperature arbitrarily were considered to have "discernible

reasons for fever," and their charts were excluded from further examination (Table II). The groups of conditions which may be associated with a temperature elevation and which were excluded were as follows: (1) diseases in which there is increased heat production, (2) diseases in which there is an impairment of heat loss, (3) physiologic temperature fluctuations, such as those associated with ovulation in menstruating women, exercise, and obstetrical labor, (4) diseases in which there is tissue injury, including mechanical injury, neoplastic disease, hematopoietic disorders, vascular accidents, diseases due to immune mechanisms, certain metabolic disorders, chemical poisons, inflammatory diseases, all infections, and degenerative diseases (Appendix A).

TABLE II. ALTERNATE FIRST ADMISSIONS TO NORTH CAROLINA MEMORIAL HOSPITAL, 1956


TOTAL FIRST ADMISSIONS IN SAMPLE
2,529 Patients or 100.0%
Patients WITH Discernible Reasons for FEVER
Patients WITH laboratory findings, diagnoses associated with fever, and/or drugs known to suppress or produce fever
2,194 patients or 86.8 per cent
Patients WITHOUT Discernible Reasons for FEVER
Patients WITHOUT laboratory findings, diagnoses associated with fever, and/or drugs known to suppress or produce fever
335 patients or 13.2 per cent
TEMPERATURE GROUP
Patients WITH initial temperature elevations
91 patients or 3.6 per cent
NO TEMPERATURE GROUP
Patients WITHOUT initial temperature elevations
244 patients or 9.6 per cent

All patients were excluded who had any of the following laboratory data recorded as abnormal: hematocrits or hemoglobins, total white counts, differential counts, sedimentation rates, C-reactive protein determinations, cultures, urinalyses, agglutinations, serologic tests for syphilis, skin tests, thyroid function tests, or any other laboratory studies that could conceivably be associated with

temperature elevations (Appendix B). All patients who had received prior to admission or during admission drugs that had pyretic or antipyretic properties were excluded (Appendix C). Patients with less than six temperature determinations were excluded.

For each patient not previously excluded by the previous criteria, the basic data recorded included: hospital number, birth date, age, sex, race, service of admission, month of admission, oral or rectal temperature determinations (axillary temperature is used only for newborn infants in this hospital), initial white count, date of onset of last menstrual period, diagnosis, first two temperatures recorded following admission with time and date of each, and last four temperatures recorded prior to discharge with time and date of each.

The mean of the first two temperatures and the mean of the last four temperatures were determined. The difference between the mean of the first two temperatures and the mean of the last four temperatures was calculated and recorded as D_1. Similarly, the difference between the first temperature following admission and the mean of the last four temperatures were calculated and recorded as D_2. Although in general the coefficient of variation of body temperature is one of the smallest known, there may be relatively wide variations between the ranges of temperature in different individuals.[13-20] In this study each individual's "normal" temperature following acclimation to hospitalization as determined by the mean of the last four temperatures prior to discharge was used as the control with which the initial temperature and the mean of the first two determinations were compared. If diurnal variation, as determined by inspection of the times at which the temperatures were taken and the patterns on successive days, or if a change from rectal to oral determination would account for the fall in temperature, the patient was excluded from the series.

Patients for whom D_1 or D_2, as described above, was 0.8° or greater were considered to have an initial elevation of temperature. These patients are referred to as the Temperature Group. Similarly, patients not previously excluded, in whom D_1 and D_2 were less than 0.8° F. were not considered to have an initial elevation of temperature and are referred to as the No Temperature Group.

FINDINGS

In this university hospital 13.2 per cent (335 patients) of the new admissions had no discernible reasons for fever (Table II). Of this group, 91 patients (27.2 per cent) had an initial temperature elevation of 0.8° F. or greater as defined in this study. Of all first admissions, this group of 91 patients represented an over-all incidence of 3.6 per cent. The range of initial temperature elevations was 0.8° F. to 2.7° F. The mean elevation was 1.15° F. and the median elevation was 1.0° F. (Fig. 1).

Of the patients without discernible reasons for fever but with an initial temperature elevation (temperature group), 38.4 per cent and 36.3 per cent were admitted on Psychiatry and Medicine, respectively. Much lower proportions were admitted on Surgery (19.8 per cent) and Pediatrics (5.5 per cent), and none were admitted on Obstetrics (Table III). The frequent association of slight

temperature elevations with labor resulted in the exclusion of many patients on this service. The distribution of the no temperature group (i.e., similar patients without an initial temperature elevation) was approximately the same. When the distribution by services of the patients without discernible reasons for fever is compared with the distribution of all first admissions (Table III), it is apparent, as would be expected, that in both the temperature group and the no temperature group, the percentages of patients are higher on the psychiatry service (38.4 per cent and 33.6 per cent) than its proportional share of first admissions, which was only 9.8 per cent. Similar percentages for the temperature group and for

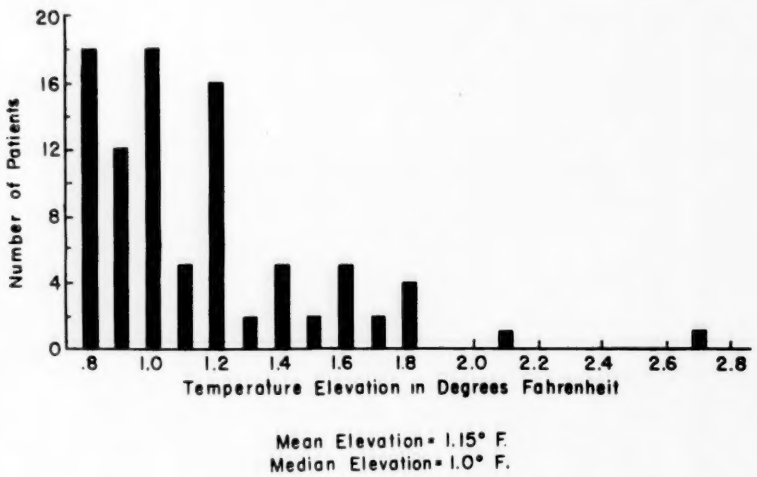


Fig. 1.—Distribution of temperature elevations in 91 patients with initial temperature elevation of 0.8° F. or higher among first admissions without discernible reasons for fever.

TABLE III. DISTRIBUTION BY SERVICES OF PATIENTS WITHOUT DISCERNIBLE REASON FOR FEVER

SERVICE	TEMPERATURE GROUP		NO TEMPERATURE GROUP		FIRST ADMISSIONS* DURING 1956 BY RANDOM SAMPLING	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Psychiatry	35	38.4	82	33.6	248	9.8
Medicine	33	36.3	71	29.1	941	37.2
Surgery	18	19.8	66	27.1	910	36.0
Pediatrics	5	5.5	23	9.4	215	8.5
Obstetrics	0	0.0	2	0.8	215	8.5
Totals	91	100.0	244	100.0	2529†	100.0

Comparison of the distribution by services of patients in the temperature group, the no temperature group, and all first admissions.

*Distribution between services determined by random sample.

†Actual number of first admissions in original sample.

all first admissions occur on the Medical and Pediatric services. The Surgical and Obstetrical services have lower percentages of patients with an initial temperature elevation than would be anticipated from their share of all first admissions. In general, the distribution by services of patients with discernible reasons for fever when compared to all first admissions suggests, as would be expected, that the proportion of "nonorganic" disease is somewhat less on Psychiatry than on the other services.

Since the records of only the patients without discernible reasons for fever were examined for an initial temperature elevation, it seems probable that the over-all true incidence of this phenomenon in a university hospital population is considerably greater than 3.6 per cent, although less than 27.2 per cent. Because of the influence of many organic factors and the necessity for employing rigid criteria in an epidemiologic study such as this, it would only be possible to determine the true incidence by carefully studying all patients with an initial temperature elevation whether or not they had discernible reasons for fever.

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When the distribution of patients without discernible reasons for fever between those in the temperature group and those in the no temperature group is examined by services (Table IV), both Psychiatry (29.9 per cent) and Medicine (31.7 per cent) have larger proportions with an initial temperature elevation than does the group as a whole (27.2 per cent).

TABLE IV. DISTRIBUTION BY SERVICES OF PATIENTS WITHOUT DISCERNIBLE REASONS FOR FEVER

SERVICE	TEMPERATURE GROUP		NO TEMPERATURE GROUP		TOTALS	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Psychiatry	35	29.9	82	70.1	117	100.0
Medicine	33	31.7	71	68.3	104	100.0
Surgery	18	21.4	66	78.6	84	100.0
Pediatrics	0	17.9	23	82.1	28	100.0
Obstetrics	0	0.0	2	100.0	2	100.0
Totals	91	27.2	244	72.8	335	100.0

Percentage of patients admitted to each service who were in the temperature group compared with the percentage of patients admitted to that same service who were in the no temperature group.

Of all first admissions to the Psychiatric service, 14.1 per cent (35 patients) had an initial temperature elevation without discernible reason, in contrast to the over-all incidence of 3.6 per cent and the similarly low incidence on the four other services (Table V). This high incidence on Psychiatry is approximately four times greater than the over-all incidence, but this is probably related to the higher proportion (47.2 per cent) of patients admitted to psychiatry without discernible reasons for fever and does not represent a greater incidence of an initial

temperature elevation among the patients admitted to psychiatry without discernible reasons for fever. As noted above, the percentages of patients without discernible reasons for fever who were admitted to psychiatry (29.9 per cent) and medicine (31.7 per cent) and of all admissions (27.2 per cent) without discernible reasons for fever are of approximately the same order of magnitude. Psychiatrists may see more patients with an unexplained initial temperature elevation then internists, but only because they see more patients without discernible reasons for fever. Among the latter group, however, internists and psychiatrists in a university hospital may expect to see initial temperature elevations in approximately the same proportions, i.e., about 30 per cent (Table IV).

TABLE V. COMPARISON OF INITIAL TEMPERATURE ELEVATION GROUP, COMPARISON GROUP, PATIENTS WITHOUT DISCERNIBLE REASONS FOR FEVER, AND FIRST ADMISSIONS AS CALCULATED FROM SAMPLE

SERVICE	A TEMPERATURE GROUP		B NO TEMPERATURE GROUP		C PATIENTS WITHOUT DISCERNIBLE REASONS FOR FEVER		D FIRST* ADMISSIONS CALCULATED FROM SAMPLE	
	NO.	PER CENT A/D	NO.	PER CENT B/D	NO.	PER CENT C/D	NO.	PER CENT
Psychiatry	35	14.1	82	33.1	117	47.2	248	9.8
Medicine	33	3.5	71	7.5	104	11.0	941	37.2
Surgery	18	2.0	66	7.2	84	9.2	910	36.0
Pediatrics	5	2.3	23	10.7	28	13.0	215	8.5
Obstetrics	0	0.0	2	0.9	2	0.9	215	8.5
Totals	91	3.6	244	9.6	335	13.2	2529†	100.0

Distribution by services of the temperature group (A), the no temperature group (B), patients without discernible reasons for fever (C), and all first admissions (D). In addition to the number of patients in each category, the percentage this number represents of the first admissions on each service is given.

*Distribution among services determined by random sample.

†Actual number of first admission in original sample.

The incidence of "emotional and mental" diagnoses (Tables V, VI, and Appendix D) was significantly* higher among patients in the temperature group (63.9 per cent) than among patients in the no temperature group (52.5 per cent), despite the presence of more Psychiatric service patients in the latter group. Appendices D and E give detailed classifications of all diagnoses in patients without discernible reasons for fever.

The incidence of an initial temperature elevation among patients without discernible reasons for fever was significantly greater in men (40/133 or 30.1 per cent) than in women (51/202 or 25.2 per cent) (Table VII). Among patients with an initial temperature elevation there were more women (51/91 or 56.0 per cent) than men (40/91 or 44.0 per cent). The difference between these figures

*The term "significant" means $P < 0.05$ and the term "highly significant" means $P < 0.01$.

and those above is due to the high percentage (202/335 or 60.3 per cent) of women among all patients without discernible reasons for fever.

The incidence of an initial temperature elevation among patients without discernible reasons for fever was greater in the 21- to 40-year age group

TABLE VI. DISTRIBUTION BY ALL DIAGNOSES CODED IN CHARTS OF PATIENTS WITHOUT DISCERNIBLE REASONS FOR FEVER

	TEMPERATURE GROUP		NO TEMPERATURE GROUP	
	NO.	PER CENT	NO.	PER CENT
"Emotional and mental" diagnoses	85	63.9	197	52.5
"Organic" diagnoses	46	34.6	174	46.4
Nondiagnostic terms	2	1.5	4	1.1
Totals	133	100.0	375	100.0

The distribution of all diagnoses coded in the hospital records of patients without discernible reasons for fever is expressed as a percentage of all diagnoses in the temperature group and again as a percentage of diagnoses in the no temperature group. The comparison of "Emotional and Mental" and "Organic" diagnoses, excluding the "nondiagnostic" terms is significant ($p < 0.05$). "Emotional and mental diagnoses" were classified in accordance with diagnostic and Statistical Manual-Mental Disorders, Washington, American Psychiatric Association, 1952.

TABLE VII. DISTRIBUTION BY SEX OF PATIENTS WITHOUT DISCERNIBLE REASONS FOR FEVER

SEX	TEMPERATURE GROUP	NO TEMPERATURE GROUP	TOTALS
	NO.	NO.	NO.
Men	40	93	133
Women	51	151	202
Totals	91	244	335

TABLE VIII. DISTRIBUTION BY AGE OF PATIENTS WITHOUT DISCERNIBLE REASONS FOR FEVER

AGE	TEMPERATURE GROUP	NO TEMPERATURE GROUP	TOTALS
	NO.	NO.	NO.
0–20	16	42	58
21–40	39	80	119
41–60	25	94	119
61+	11	28	39
Totals	91	244	335

(39/119 or 32.8 per cent) than in the younger and older groups (Table VIII). The highest proportion of patients in the temperature group occurred in the 21- to 40-year age group (39/91 or 42.8 per cent). Lower proportions occurred in the older and younger groups. Among patients in the no temperature group, the highest proportion (94/244 or 38.5 per cent) occurred in the 41- to 60-year age group. These differences between the 21- to 40-year and the 41- to 60-year age groups are significant.

TABLE IX. DISTRIBUTION BY AGE AND SEX OF PATIENTS WITHOUT DISCERNIBLE REASONS FOR FEVER

SEX	AGE	TEMPERATURE GROUP		NO TEMPERATURE GROUP		TOTALS	
		NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Females	0–20	5	18.5	22	81.5	27	100.0
	21–40	21	27.3	56	72.7	77	100.0
	41–60	18	24.3	56	75.7	74	100.0
	61+	7	29.2	17	70.8	24	100.0
Males	0–20	11	35.5	20	64.5	31	100.0
	21–40	18	42.9	24	57.1	42	100.0
	41–60	7	15.6	38	84.4	45	100.0
	61+	4	26.7	11	73.3	15	100.0

TABLE X. DISTRIBUTION BY RACE OF PATIENTS WITHOUT DISCERNIBLE REASONS FOR FEVER

RACE	TEMPERATURE GROUP NO.	NO TEMPERATURE GROUP NO.	TOTALS NO.
Negro	7	17	24
White	84	227	311
Totals	91	244	335

Further analysis of the age distributions by sexes (Table IX) indicates that the differences in distribution of females in the four age groupings are not significant. For men, however, in each of the four age categories, the proportions in the temperature group as contrasted with the proportions in the no temperature group are significant. The distribution of men in the 21- to 40-year age group compared with the 41- to 60-year age group in the temperature group and no temperature group is highly significant.

The incidence of an initial temperature elevation among patients without discernible reasons for fever was almost equal in colored (7/24 or 29.1 per cent) and white (84/311 or 27.1 per cent) patients (Table X). The proportion of colored patients (7/91 or 7.7 per cent) among patients in the temperature group was almost equal to the proportion of colored patients (17/244 or 7.0 per cent) among patients in the no temperature group.

DISCUSSION

No careful study was found in the literature of the over-all incidence of "psychogenic fever" among patients admitted to a general or university hospital; hence the over-all incidence as determined by this study cannot be compared with other values. The incidence (27.2 per cent) of patients with an initial elevation of temperature among patients without discernible reasons for fever might possibly be compared with the incidence (36 per cent) of temperature elevations above 99.0 per cent F. among 30 patients diagnosed as having "neurocirculatory asthenia" determined by Friedman.[7] However, since the methods of study were different, the determinations are not really comparable. Wynn's[6] study showing a rise in temperature above 99° F. in 67 per cent of 324 men being examined for the draft might be compared with our incidence (27.2 per cent) among patients without discernible reasons for fever. Again, the methods and populations in the two studies were different, and caution must be exercised in making comparisons.

The higher incidence (32.8 per cent) of an initial temperature elevation among patients without discernible reasons for fever in the 21- to 40-year age group might be compared with the high incidence (66.6 per cent) among 100 patients with long-continued, low grade fever in the 20- to 40-year age group found by Kintner and Rowntree.[9] The methods, populations, and characteristics of the temperature elevations in this study were different from the present one and therefore greatly limit comparison.

Kintner and Rowntree[9] found that 72 per cent of their group with fever were females in contrast to our figure of 56 per cent. However, although there were more women (60.3 per cent) in our series without discernible reasons for fever, the proportion of the women with fever in this group was 25.5 per cent and the proportion of the men was 30.1 per cent, a significant difference.

From the data of this study it would appear that an initial temperature elevation of 0.8° F. or greater in a patient without discernible reasons for fever may be an important diagnostic clue to the presence of "psychogenic fever" and associated underlying emotional disturbances. The high proportion of patients without discernible reasons for fever who in fact do have this initial elevation on medicine (31.7 per cent) and psychiatry (29.9 per cent) suggests that general physicians, internists, and psychiatrists should have a high index of suspicion for this phenomenon. Such an initial temperature elevation appears in general to be more common in men than in women and in young adults aged 21 to 40 than in younger or older persons. It is most prevalent in young men aged 21 to 40. There were no racial differences observed. Organic causes of fever

should always be kept in mind, but a characteristic spontaneous fall of temperature after a day or two in the hospital distinguishes this phenomenon from many forms of organic fever.

SUMMARY

1. Previous limited studies of the incidence of psychogenic fever are reviewed. The charts of alternate first admissions to a university hospital were examined, and all patients with any possible organic or drug factors modifying their temperatures were excluded.

2. The incidence of an initial temperature elevation of 0.8° F. or greater occurring immediately following first admission in patients without discernible cause for fever was found to be 3.6 per cent of all first admissions. The incidence of initial temperature elevation, as defined above, among all patients without discernible reason for fever was 27.2 per cent. The true incidence of this phenomenon is probably greater than 3.6 per cent and less than 27.2 per cent.

3. The incidence on medicine and psychiatry was slightly higher i.e., 31.7 per cent and 29.9 per cent, respectively, and on the other services was lower, i.e., surgery, 21.4 per cent; obstetrics, 0.0 per cent and pediatrics, 17.9 per cent. The over-all proportion of first admissions to the hospital without discernible reasons for fever was 13.2 per cent, but on psychiatry this proportion was 47.2 per cent, and there were lower proportions on other services, i.e., medicine, 11.0 per cent, surgery, 9.2 per cent, obstetrics, 0.9 per cent, and pediatrics, 13.0 per cent.

4. The incidence of an initial temperature elevation in patients without discernible reasons for fever among all first admissions to psychiatry was 14.4 per cent or four times greater than the incidence of this initial temperature elevation on all other services, i.e., medicine, 3.5 per cent, surgery 2.0 per cent, obstetrics, 0.0 per cent, pediatrics, 2.3 per cent, and for all first admissions, 3.6 per cent. Psychiatrists see more patients with an unexplained initial temperature elevation than do internists.

5. The phenomenon of an initial unexplained temperature elevation is much more frequently observed in men in the age group 21 to 40 than in other population groups.

6. The recognition of a characteristic spontaneous fall of temperature after a day or two in the hospital without evidence of organic disease or the administration of a drug should suggest the possibility that the patient has "psychogenic fever" and associated underlying emotional problems.

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APPENDIX A

CONDITIONS ASSOCIATED WITH FEVER

I. Conditions in which there is increased heat production

- A. Thyrotoxicosis
- B. Convulsions

II. Conditions in which there is impairment of heat loss

- A. Congestive heart failure
- B. Auricular fibrillation
- C. Paroxysmal tachycardia
- D. Extensive skin diseases such as ichthyosis
- E. Congenital absence of sweat glands
- F. Gastrointestinal hemorrhage
- G. Heat stroke and heat exhaustion

III. Conditions in which there is tissue injury

- A. Mechanical injury—crushing injuries, extensive surgery, cystoscopy, gastroscopy, bronchoscopy, fracture fevers, head injuries, burns
- B. Neoplastic diseases
  1. Tumors of the kidney
  2. Tumors of the gastrointestinal tract (stomach, colon, liver, pancreas, gall bladder, and bile duct)
  3. Retroperitoneal tumors (Hodgkin's disease and sarcoma)
  4. Tumors of lungs and breasts
  5. Tumors of bones
  6. Tumors of brain
- C. Hematopoietic disorders
  1. Acute hemolytic crises
  2. Severe pernicious anemia

3. Agranulocytosis
4. Leukemia
5. Aplastic anemia
6. Infectious mononucleosis
7. Osseous myeloid dysplasia
8. Plasmosarcoma
9. Henoch-Schonlein or allergic purpura
10. Thrombocytopenic purpura
11. Hemophilia
12. Scurvy

D. Vascular accidents
1. Cardiac infarction
2. Hemorrhages
3. Embolism to various organs
4. Thrombosis
5. Septal infarction

E. Diseases due to immune mechanisms
1. Collagen diseases
a. Rheumatic fever
b. Disseminated lupus erythematosus
c. Scleroderma
d. Rheumatoid arthritis
e. Periarteritis nodosa
f. Dermatomyositis
g. Thromboangitis obliterans
2. Drug fevers
a. Sulfonamides
b. Arsenicals
c. Iodides, bromides
d. Thiouracils
e. Barbiturates
f. Phenolphthalein
g. Belladonna
h. Morphine
i. Dinitrophenol
j. Procaine amide
k. Antibiotics (allergic reactions)
l. Alcohol
3. Serum sickness
4. Allergic fever
5. All foreign protein reactions—transfusions, pyrogens in rubber tubing, pyrogens produced by Aerobacter cloacae in inspired cotton fibers

F. Certain metabolic disorders
1. Gout
2. Porphyria
3. Hyperthyroidism and thyroid storm
4. Cirrhosis of liver and acute postoperative necrosis of the liver
5. Amyloid disease
6. Idiopathic familial lipemia
7. Diabetic acidosis
8. Dehydration of body tissues
9. Hypothyroidism

G. Chemical poisons
1. Metal fume fever
2. Gold poisoning

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3. Carbon monoxide poisoning

H. Inflammatory diseases
   1. Ulcerative colitis
   2. Regional enteritis
   3. Relapsing febrile nodular nonsuppurative panniculitis
   4. Duodenal ulcer
   5. Verrucous nonbacterial endocarditis

I. All infections
   1. Bacterial
      a. Pneumococcal infections
      b. Hemolytic streptococcal infections
      c. Meningococcal infections
      d. Gonococcal infections
      e. Colon and Aerogenes infections
      f. Staphylococcal infections
      g. Proteus and Pseudomonas infections
      h. Friedlander bacillus infections
      i. Salmonella infections
      j. Shigella infections
      k. Cholera
      l. Hemophilus affections
      m. Other gram-negative bacillary infections
         (1) Brucellosis
         (2) Tularemia
         (3) Plague
         (4) Glanders
         (5) Melioidosis
      n. Anaerobic infections
         (1) Anaerobic streptococcal infections
         (2) Bacteroides infections
      o. Miscellaneous bacterial infections
         (1) Anthrax
         (2) Streptobacillus moniliformis infection
         (3) Bartonellosis
         (4) Granuloma inguinale
      p. Diseases due to toxin-producing bacteria
         (1) Diphtheria
         (2) Tetanus
         (3) Botulism
      q. Mycobacterial infections
   2. Fungus infections
      a. Involving internal organs
         (1) Actinomycosis
         (2) Nocardiosis
         (3) Cryptococcosis
         (4) Moniliasis
         (5) North American blastomycosis
         (6) South American blastomycosis
         (7) Coccidioidomycosis
         (8) Histoplasmosis
      b. Involving skin and subcutaneous tissues
         (1) Sporotrichosis
         (2) Chromoblastomycosis
         (3) Maduromycosis
      c. Involving only skin, hair, or nails
         (1) The dermatomycoses

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3. Spirochetal infections
   a. Syphilis
   b. Yaws
   c. Pinta
   d. Leptospiral infections
   e. Relapsing fever
   f. Rat-bite fever
   g. Fusospirochetosis
4. Rickettsial infections
   a. Rocky mountain spotted fever
   b. Rickettsialpox
   c. African tick-borne fever
   d. Murine typhus fever
   e. Epidemic typhus fever
   f. Brill's disease
   g. Scrub typhus
   h. Q fever
5. Viral infections
   a. Of respiratory tract
      (1) Influenza
      (2) Psittacosis
      (3) Common respiratory disease
   b. Exanthematous viral infections
      (1) Rubeola
      (2) Rubella
      (3) Varicella
      (4) Smallpox and vaccinia
      (5) Dengue
   c. Neurotropic viral infections
      (1) Lymphocytic choriomeningitis
      (2) Viral encephalitides
      (3) Poliomyelitis
      (4) Rabies
      (5) Herpes zoster
      (6) Mumps
   d. Viral infections of the liver
      (1) Viral hepatitis
      (2) Yellow fever
   e. Miscellaneous viral infections
      (1) Coxsackie viral infections
      (2) Herpes simplex
      (3) Phlebotomus fever
      (4) Foot-and-mouth disease
      (5) Lymphogranuloma venereum
      (6) Colorado tick fever
      (7) Cat-scratch disease
      (8) Hemorrhagic fever
6. Protozoan infections
   a. Amebiasis
   b. Malaria
   c. Leishmaniasis
   d. Toxoplasmosis
7. Diseases caused by nematodes
   a. Hookworm disease

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b. Creeping eruption
c. Strongyloidiasis
d. Trichostrongyliasis
e. Ascariasis
f. Trichuriasis
g. Enterobiasis
h. Trichinosis
i. Filariasis
j. Onchocerciasis
k. Loiasis
l. Dracunculiasis

8. Disease caused by trematodes
   a. Schistosomiasis
   b. Schistosome dermatitis
   c. Clonorchiasis
   d. Opisthorchiasis
   e. Fascioliasis
   f. Fasciolopsiasis
   g. Paragonimiasis
9. Diseases caused by cestodes
   a. Diphyllobothriasis latum and sparganosis
   b. Taeniasis saginata
   c. Taeniasis solium
   d. Echinococciasis
   e. Hymenolepiasis nana

J. Neurogenic disorders
   1. Spinal poikilothermia
   2. Inhibition or paralysis of thermotaxic centers
      a. Anesthesia
      b. Acute increase of intracranial pressure
   3. Lesions of thermotaxic centers

K. Degenerative diseases
   1. Multiple sclerosis
   2. Fibroid degeneration

IV. Physiological Associations with temperature elevations and variations
   A. Strenuous exercise
   B. Digestion
   C. First trimester of pregnancy
   D. Obstetrical labor
   E. Menstrual cycle

APPENDIX B

LABORATORY CRITERIA EMPLOYED

I. Range of acceptable agglutinations
   A. Psittacosis—1:8 or less
   B. Primary atypical pneumonia—1:16 or less
   C. Influenza—absence of fourfold rise in titer
   D. Typhoid "O"—1:40 or less
   E. Brucellosis—1:20 or less

II. Acceptable hematologic values

A. Corrected sedimentation rates 15 mm./hour or less
B. Hematocrit
   1. Adult males—40.0 to 54.0 per cent
   2. Adult females—37.0 to 47.0 per cent
C. Hemoglobin
   1. Adult males—14.0 to 18.0 Gm.
   2. Adult females—12.0 to 16.0 Gm.
D. White blood cells—4,000 to 12,000/cu. mm.
E. Differential counts
   1. Neutrophils—57 to 67 per cent
   2. Eosinophils—1 to 3 per cent
   3. Basophils—0 to 1 per cent
   4. Lymphocytes—21 to 38 per cent
   5. Monocytes—3 to 7 per cent

Note: Variation from above normals were accepted in pediatric patients according to age of patient and normal values for that age as listed in Ham.[21]

III. Normal values for thyroid function tests

A. Protein bound iodine—4 to 8 gamma per cent
B. I^{131} uptake—15 to 45 per cent
C. Basal metabolic rate—plus or minus 15 per cent
D. Butanol extractable iodine—4 to 8 gamma per cent

IV. "Positive" laboratory findings assumed to be associated with fever

A. Any cultures reported positive for pathogenic bacteria
B. Any positive serologic test for syphilis
C. Any positive skin test (tuberculin, histoplasmin, blastomycin, coccidioidin)
D. Any positive C-reactive protein determinations
E. Any urinalysis reported to contain more than 0 to 10 WBC per high power field and/or more than 0 to 5 RBC per high power field.

APPENDIX C

POTENTIALLY PYRETIC AND ANTIPYRETIC DRUGS

I. Drugs with antipyretic action
   - Acetanilid
   - Acetophenetidin
   - Acetylsalicylic acid
   - Adrenocortical hormones
   - All antibiotics
   - Aminopyrine
   - Antipyrine
   - Chlorpromazine
   - Cinchophen
   - Colchicine
   - Dipyrone
   - Ergot alkaloids
   - Hydroxyphenylcinchoninic acid
   - Neocinchophen
   - p-Acetamidophenyl salicylate
   - Phenyl salicylate
   - Phenylbutazone
   - Reserpine
   - Salicylamide
   - Sodium resorcylate
   - Sodium salicylate

II. Drugs that may be associated with fever
   - Alcohol
   - Antibiotics (allergic reactions)
   - Arsenicals
   - Barbiturates
   - Belladonna
   - Dinitrophenol
   - Iodides and bromides
   - Morphine
   - Phenolphthalein
   - Procaine amide
   - Sulfonamides
   - Thiouracils

APPENDIX D

DISTRIBUTION OF EMOTIONAL AND MENTAL DISORDERS BY ALL DIAGNOSES CODED IN CHARTS OF PATIENTS WITHOUT DISCERNIBLE REASONS FOR FEVER

DIAGNOSES	TEMPERATURE GROUP		NO TEMPERATURE GROUP	
	NUMBER	PER CENT	NUMBER	PER CENT
I. Acute brain disorders	1	1.2		
Acute alcoholism	1			
II. Chronic brain disorders	4	4.7		
Cerebral arteriosclerosis	4			
III. Mental deficiency				
IV. Psychotic disorders	11	12.9	26	13.2
Involutional psychotic reactions	1		4	
Affective reactions	4		10	
Schizophrenic reactions	6		10	
Paranoid reactions			2	
V. Psychophysiologic autonomic and visceral disorders	30	35.3	79	40.1
Skin reactions	1			
Musculoskeletal reactions	2		5	
Respiratory reactions			1	
Cardiovascular reactions	7		10	
Gastrointestinal reactions	8		30	
Genitourinary reactions	2		3	
Endocrine reactions, obesity, exogenous hirsutism	1		10	
Nervous system reactions	7		20	
Reactions of organs of special sense	2			
VI. Psychoneurotic disorders	25	29.4	60	30.5
Anxiety reactions	7		19	
Dissociative reactions	1		3	
Conversion reactions	7		14	
Phobic reactions	1		1	
Obsessive compulsive reactions	1		2	
Depressive reactions	7		22	
Psychoneurotic reactions, other	1			
VII. Personality disorders	14	16.5	29	14.7
VIII. Transient situational personality Disorders			3	1.5
Totals	85	100.0	197	100.0

(*Appendix E on next page.*)

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APPENDIX E

DISTRIBUTION OF ORGANIC DISEASES BY ALL DIAGNOSES CODED IN CHARTS OF PATIENTS WITHOUT DISCERNIBLE REASONS FOR FEVER

CATEGORIES	TEMPERATURE GROUP		NO TEMPERATURE GROUP	
	NUMBER	PER CENT	NUMBER	PER CENT
I. Skin	3	6.5	7	4.0
II. Special Senses	6	13.0	17	9.8
III. Respiratory	3	6.5	5	2.9
IV. Circulatory	7	15.2	22	12.5
V. Gastrointestinal	4	8.7	14	8.0
VI. Genitourinary	7	15.2	25	14.3
VII. Musculoskeletal	10	21.8	31	17.7
VIII. Neurologic	5	10.9	30	17.2
IX. Hematopoietic	0	0.0	2	1.2
X. Endocrine	1	2.2	20	11.8
XI. Fever unknown origin	0	0.0	1	0.6
Totals	46	100.0	174	100.0

DISTRIBUTION OF NONDIAGNOSTIC TERMS CODED IN CHARTS OF PATIENTS WITHOUT DISCERNIBLE REASONS FOR FEVER

NONDIAGNOSTIC TERMS	TEMPERATURE GROUP		NO TEMPERATURE GROUP	
	NUMBER	PER CENT	NUMBER	PER CENT
I. Diagnosis deferred			2	50.0
II. Observation			1	25.0
III. No disease	1	50.0	1	25.0
IV. Undiagnosed disease	1	50.0		
Totals	2	100.0	4	100.0

A STUDY OF THE ADRENAL STATUS IN HYPERTENSION

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WHAT role the adrenal glands may play in essential human hypertension is controversial. Opinions vary from a hypothesis that it is the adrenocortical reaction to life situations that may be responsible for high blood pressure and other illnesses to the statement that aside from the prerequisite of their presence the adrenals have no evident connection with essential hypertension.[17] Despite much current interest in the relationship of adrenal function to elevated blood pressure in human beings, there are few incontrovertible facts.

Pathologic studies of the adrenal cortex and medulla in hypertension have been at variance as to what abnormalities are observed. No large series of cases has been analyzed statistically. Potentially useful information contributed by the present study includes (1) demonstration of a significantly increased statistical association between hypertension and genuine adrenocortical adenomas, (2) observation of frequent nodular protrusions of the adrenal cortex into the adjacent medulla and peripheral capsule accompanying hypertension, (3) greater cell densities in the outer adrenocortical zone of adrenalectomy specimens in hypertension, and (4) failure to confirm a gross adrenal hypertrophy as characteristic of hypertension.

MATERIALS AND METHODS

The weights, estimated lipoid content, and structural abnormalities of adrenal glands were studied in 78 hypertensive patients who had a therapeutic unilateral or bilateral adrenalectomy. There were 43 men and 35 women included (Table I). From the laboratory files, records of 220 autopsied cases of persons with hypertension were also obtained, many of whom had died with congestive heart failure, and this was the major cause of death in 48 cases.

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TABLE I. AGE AND SEX DISTRIBUTIONS OF 78 ADRENALECTOMIZED HYPERTENSIVE PATIENTS, 220 AUTOPSIED CASES WITH HYPERTENSION AND 220 AUTOPSIED CASES WITH NORMAL BLOOD PRESSURE

AGE (YEARS)	ADRENALECTOMIZED		AUTOPSIED			
			HYPERTENSION		NORMOTENSION	
	M	F	M	F	M	F
16–30	2	5	3	3	8	16
31–40	10	9	4	6	15	20
41–50	26	16	18	10	21	20
51–60	5	4	29	18	27	28
61–70	0	1	29	34	21	8
71–80	0	0	33	17	13	16
81–99	0	0	7	9	5	2

Hypertension was of the essential type in 156 cases, associated with pyelonephritis in 40, with glomerulonephritis in 8, and with both pyelonephritis and glomerulonephritis in 3. In 8 cases there were prominent renal infarcts. Also, there was one case each of hypertension accompanied by polycystic kidneys, nodular intercapillary glomerulosclerosis, severe hydronephrosis, renal cell carcinoma, and pulmonary carcinoma with chronic cor pulmonale. No differences in the adrenal changes were observed that could be correlated with the different subtypes of hypertension. Special types of hypertension were not included, such as those accompanying aortic coarctation, Cushing's syndrome, pheochromocytoma, or unilateral renal disease. Cases with cardiac valvular disease were also excluded. All cases considered hypertensive either had had (a) consistent blood pressure level of 150/100 mm. Hg or higher, (b) heart weights of 500 Gm. for men, or 450 Gm. for women, or more, without other major cardiac abnormalities, or (c) both.

For comparison a series of 220 normotensive autopsied cases was collected, with previous blood pressure levels of 140/90 mm. Hg or less, and with heart weights equal to or less than 400 Gm. for men or 350 Gm. for women. Age and sex distributions are shown in Table I.

The gross adrenal weights, lipoid content of cortex as judged by the abundance of cytoplasmic vacuoles in paraffin sections and the sudanophilic staining of frozen sections, the cell densities per 10,000 square micra in each adrenocortical zone, the incidence of cortical nodules and adenomas, and the thickness of the medullary muscular veins were determined and compared for the two autopsied series. All studies were not performed on each case. Histochemical procedures for succinic dehydrogenase were carried out on fresh adrenal tissue from 30 patients, including 10 persons with hypertension, using the TTC reagent and technique of Shorr, Zweifach, and Black.[20]

RESULTS

Adrenal Adenomas.—In 45 autopsied cases of the 220 with hypertension (20 per cent), a single prominent gross and microscopic adrenocortical adenoma

was found, ranging from 1.5 to 10.5 cm. in diameter. Adenomas were defined as spherical or ovoid nodules of adrenocortical tissue without identifiable zonation, composed of cords and nodules of cells that were intertwined and ordinarily not oriented in lines. Adenomas often were not encapsulated, but they were usually well demarcated from the adjacent uninvolved adrenal cortex, since the normal adrenocortical cells were usually zonated, smaller, of more uniform size, and were compressed by the adenoma cells (Fig. 1). There were 16 true adenomas among the 78 adrenalectomy specimens (21 per cent). In the control series adenomas were present in 4 of 220 cases (1.8 per cent), an incidence similar to those reported in two unselected series totaling 16,437 autopsies.[2,15] Adrenocortical adenomas thus were observed in association with hypertension at about 10 times the expected incidence.

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Fig. 1.

Fig. 2.

Fig. 1.—Section of an adrenocortical adenoma, 1.3 cm. in greatest diameter, removed at operation for hypertension. Note the large lobulated cords of adenoma cells, and the contrast in staining of the compressed uninvolved adrenal cortex along the right side. (Hematoxylin and eosin, S-51-1727B, × 5.)

Fig. 2.—Cortical nodules at upper left and lower right corners, demonstrating encapsulation, zonation, and smaller size, from an adrenalectomy specimen. (Hematoxylin and eosin, S-55-1105D, ×5.)

Three cases of primary aldosteronism were recognized and adrenal adenomas, 1.0, 2.1, and 3.5 cm. in diameter, were resected. Grossly they were encapsulated, bright yellow, and homogeneous. Microscopically, these adenomas were composed of cords and nodules of lipid-rich cells, some of which showed unusual cytoplasmic swelling. The architecture of the three adenomas with aldosteronism resembled that of the zona fasciculata.[21] Functional activities of the other adenomas were not identified.

Cortical Nodules.—Well-demarcated, spherical, usually encapsulated cell masses of adrenal cortex, smaller and more numerous than the genuine adenomas, were found located either in the cortex, the capsule, or in the periadrenal fat. Their usual diameters were 0.5 to 0.8 cm. Cortical nodules were defined as small spherical masses of adrenal cortex that often showed zonation into a glomerulosa and fasciculata, and usually there was an architectural orientation closely resembling the normal adrenal cortex. Nodules were encapsulated as a rule but

ordinarily did not compress, distort, or affect the architecture of the adjacent uninvolved adrenal tissue (Fig. 2). There was no sharp distinction between a cortical nodule and a miniature cortical adenoma, but cortical nodules were more frequently multiple. They have usually been regarded as minor foci of either accessory or hyperplastic adrenal cortex, formed either during embryonic life or by subsequent growth.

In the autopsied hypertensive group 82 of the 120 cases scrutinized (68 per cent) had cortical nodules compared to 50 of 120 normotensive cases (42 per cent). Twenty-three of the 78 adrenalectomy cases (29 per cent) had adrenocortical nodules. A discrepancy was evident in the frequency of cortical nodules between hypertensive cases at adrenalectomy and autopsy, suggesting enhanced nodule development late in the patients' courses.

Fig. 3.—Adrenalectomy specimen from a case of essential hypertension, demonstrating the sudanophilic lipoid, which appears black. At the top is an extra-adrenal encapsulated cortical nodule. The cortical architecture is slightly nodular, and the small nodules are less sudanophilic than the unaltered cortex. In the lower portion is the unstained adrenal medulla, penetrated by masses of sudanophilic adrenocortical cells. (Frozen section, sudan stain, S-55-3380, × 75.)

In the autopsied cases, adrenal tissue stained for lipoid from hypertensive persons commonly demonstrated multiple unencapsulated sudanophilic adrenocortical nodules bulging inward into the medulla, as well as outward through the peripheral fibrous capsule (Fig. 3). Comparable centripetal hyperplastic overgrowths of adrenal cortex also were recognized in one-third of the glands from adrenalectomy operations in hypertension, even in paraffin sections. Such intramedullary cortical nodules were seen in less than 10 per cent of normotensive control adrenal glands.

Cell Counts.—Analyses were made on 55 cases and recorded as the number of nucleated cells per 10,000 square micra (Table II). One salient fact emerged.

There were statistically significant greater cell densities, reflecting smaller cell sizes, in the zona glomerulosa of the glands removed surgically in hypertensive patients, when compared with hypertensive or normotensive autopsied cases by t-test ($P < 0.05$). In accordance with the conclusions of Deane and coworkers,[4,5] this would reflect a relative inactivity of the outer cortical zone in adrenalectomy specimens from hypertensive persons.

TABLE II. ADRENOCORTICAL CELL DENSITIES, EXPRESSED AS NUCLEATED CELLS PER 10^3 SQUARE MICRA
(Mean ± Standard Deviation)

	CASES	ZONA GLOMERULOSA	ZONA FASCICULATA	ZONA RETICULARIS
Hypertension (autopsy)	30	36.2 ± 8.7	24.1 ± 7.1	17.7 ± 6.6
(surgical)	14	66.7 ± 10.5	32.4 ± 5.7	25.7 ± 6.5
Normotension	11	32.5 ± 7.7	18.8 ± 6.0	17.7 ± 6.3

TABLE III. RATIO OF WALL THICKNESS TO LUMEN DIAMETER IN HYPERTENSION AND NORMOTENSION

VEINS		HYPERTENSION	NORMOTENSION
NUMBER MEASURED*	DIAMETER (RANGE IN μ)		
21,3	200–299	0.207	0.179
32,30	300–399	0.198	0.257
31,49	400–499	0.194	0.106
37,31	500–599	0.176	0.158
42,59	600–699	0.173	0.153
35,31	700–799	0.184	0.194
40,34	800–899	0.181	0.103
26,19	900–999	0.162	0.197
14,6	1,000–1,099	0.232	0.187
55,67	1,100–2,100	0.227	0.206

*First figure = hypertensive group; second figure = normotensive group.

Other Morphologic Observations.—Mean adrenal weights and their standard deviations were found to be 6.1 ± 2.0 Gm. for adrenalectomy specimens, 7.9 ± 2.0 Gm. for normotensive, and 8.8 ± 2.7 Gm. for hypertensive cases at autopsy. There was no significant difference between the mean weights of different groups.

The outer fibrous capsules averaged 73.7 μ in thickness in 120 hypertensive autopsied cases, and 89.7 μ in equal number of controls, a nonsignificant difference.

Cortical lipid content, judged by the extent of vacuolization in paraffin sections and sudan staining of equal numbers of hypertensive and control cases, differed slightly. About twice as many hypertensive cases (70 per cent) had abundant adrenocortical lipid at autopsy as the normotensive controls (34 per cent).

Medullary vein wall thickness was measured in 676 instances from 168 patients, and the ratios of wall thickness to lumen diameter were computed (Table III). Statistical comparisons, using rank test methods, showed no significant increase in the wall thickness in hypertension, in contradistinction to findings in two published series.[9,10] No cytologic peculiarities of medullary cells in hypertension were identified.

Histochemistry.—An attempt was made to confirm the report of Shorr, Zweifach, and Black[20] that the red diformazan reaction with triphenyltetrazolium chloride (TTC) in the adrenal cortex of hypertensive cases was not suppressed by enzyme inhibitors, such as fluoride. In general, as reported by others, the TTC reaction in fresh human adrenal tissue is relatively weak and appears to be adversely affected by the postmortem time interval and unknown factors.[8] Equal numbers of hypertensive and normotensive cases were tested and failed to show any definite inhibition of formazan formation after sodium fluoride inhibition.

Fig. 4.

Fig. 5.

Fig. 4.—Portion of adrenal cortex of an autopsied hypertensive case. Both an extracapsular nodule and the nodular portion of the cortex shown in the lower part of the illustration are strongly positive for succinic dehydrogenase. (TTC technique with sodium fluoride, A-56-16, × 150.)

Fig. 5.—A histochemical procedure for succinic dehydrogenase shows moderately dark staining of the adrenal cortex, except for the round nodule. The nodule was strongly sudanophilic. The medulla is unstained. (TTC technique with sodium fluoride, S-55-3380, × 150.)

The observation of most interest with the TTC reaction for demonstrating succinic dehydrogenase concerned the adrenocortical nodules, both intra- and extracapsular. By the formazan and sudanophilic reactions these nodules were usually out of phase with the rest of the adrenal cortex. The nodules most frequently were comparatively poor in sudanophilic lipoid, and stained relatively strongly with TTC (Fig. 4). Occasionally when the majority of the cortex was

lipoid-depleted and took a moderately strong TTC stain, the nodule was found rich in lipoid and unstained by TTC (Fig. 5). A localized abnormality of metabolism associated with adrenocortical nodularity seems likely.

DISCUSSION

Judging from the review article of Sapeika[16] 10 years ago, there would be a strong suspicion of an increased frequency of adrenocortical hyperplasia or adenomas and a greater mean adrenal weight accompanying hypertension. When the tabulated data are analyzed individually and by the more sophisticated statistical methods now being used in medicine, only adrenocortical adenomas are found significantly more often in hypertensive than in normotensive or unselected control series.[1,6,7,12] Dempsey's study[6] was one of the first to compare the mean adrenal weights in hypertensive and normotensive autopsied cases by statistical techniques and to point out that any increase of adrenal weight with hypertension was insignificant. The recent report of Paul and coworkers[13] has established pre-existent congestive heart failure as one factor likely to be increasing the adrenal weight of hypertensives at autopsy.

Since 1948, Holmes, Moon, and Rinehart,[11] Schroeder and Davies,[18] and Dawson[3] have found increased adrenal weight, cortical nodularity, adenomas, or hyperplasia to be more common in hypertensives but did not establish this tendency as statistically valid. The unproved assumption of increased adrenal weight and consequently inferred hyperfunction in hypertension has been maintained for about 50 years.

The true adrenocortical adenomas, found in the present series in one-fifth of hypertensive cases, are of potential clinical significance. Only 3 of these 61 adenomas (5 per cent) were recognized clinicopathologically as functional tumors of etiologic importance in hypertension, with aldosterone hypersecretion. In this series the hormonal activities of 95 per cent of the adrenocortical adenomas found accompanying hypertension were not identified, leaving ample opportunities for future steroid research.

In most adrenalectomy specimens from patients with essential hypertension, cell counts demonstrated no hints of hyperactivity of either zona glomerulosa or fasciculata. In fact, the glomerulosal cells instead were relatively close-packed, with an inferred hypoactivity of the type observed to occur when the intercellular fluid is comparatively rich in sodium.[4,14] From the viewpoint of these cell counts, corticoids are not likely to be implicated in causing human essential hypertension. Medullary hyperfunction of adrenal glands in hypertension could also not be inferred from the present observations.

Failure to demonstrate significantly increased adrenal weights accompanying hypertension does not necessarily exclude an overgrowth of one component of this compound endocrine gland at the expense of others. If adrenocortical adenomas, cortical nodules, and nodular cortical protrusions are all regarded merely as different manifestations of adrenocortical overgrowth, then over 80 per cent of adrenalectomized or autopsied hypertensive cases demonstrated excessive cortical growth, compared to about 44 per cent of the control cases. More re-

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fined methods of analyzing the various adrenal components would be necessary to establish the importance of adrenocortical tissue growth activity accompanying hypertension, and its primary or secondary role. The dehydrogenase reactions employed have shown that there is some unexplained alteration of metabolism present in the adrenocortical nodules of hypertensive persons.

Of all the endocrine glands studied in human hypertension, the adrenal gland (and particulary its cortex) seems to have the closest and most important relationship to abnormal elevations of blood pressure.[19] One may hope that further analyses of its hormones may eventually explain the functional changes inferred from these morphologic investigations.[17]

SUMMARY

Structural changes were studied in adrenal glands from 78 adrenalectomized hypertensive patients and 220 hypertensive patients examined at autopsy. The findings were compared with those from 220 normotensive autopsied cases. Adrenocortical adenomas were ten times more frequent in hypertensive than in normotensive persons. Only 5 per cent of the adenomas were identified as producing aldosterone. Cell densities of the zona glomerulosa in hypertensive adrenalectomy material were significantly greater than in autopsied normotensive and hypertensive cases, possibly reflecting a relative hypoactivity of the outermost cortical zone. Nodular overgrowths of adrenal cortex were about twice as frequent in hypertensive as in normotensive persons, and dehydrogenase activity of the nodules reflected an abnormality of their metabolism. Adrenal weights, lipoid content, venous wall thickness, and other morphologic aspects investigated were not significantly different in the hypertensive and control series.

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THE L. E. PHENOMENON AND SYSTEMIC LUPUS ERYTHEMATOSUS

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SINCE the description by Hargraves, Richmond, and Morton[1] of characteristic morphologic changes in leukocytes of incubated bone marrow specimens, several reports have appeared considering the occurrence of these changes in systemic lupus erythematosus (S.L.E.) and other diseases. It was first thought that the L.E. cell and rosette were specific for S.L.E. However, during the past 8 years several reports have appeared describing the L.E. cell and rosette formation in diseases other than lupus erythematosus. As a result of these findings many believe the L.E. cell to be not specific or diagnostic for lupus erythematosus. This controversy prompted us to analyze all L.E. tests performed in our laboratory during the past 2 years, and to search for the L.E. phenomenon in those diseases in which it has been reported to occur.

METHODS

Technique of L.E. Test.—L.E. preparations were performed on incubated heparinized,[1] defibrinated,[2] or clotted[3] blood and bone marrow samples. Most of the preparations were performed by a slightly modified method* of the technique described by Zimmer and Hargraves.[3] Bone marrow preparations were allowed to clot and incubate 2 hours, after which adequate preparations containing intact cells could be made.

Definition of the L.E. Phenomenon.—Characteristics of the L.E. cell and L.E. phenomenon (Fig. 1) have been described by Hargraves, Richmond, and Morton[1] and need not be repeated here. A test was considered positive whenever L.E. cells with or without rosette formation were present. When preparations contained a sufficient cell concentration the L.E. cells present were usually numerous and easily seen with a high-dry magnification (Fig. 1, *C*). In our experience it has not been necessary to spend a great deal of time looking for L.E. cells. When the cell concentration on the slide was small, the chances of

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*To be published.

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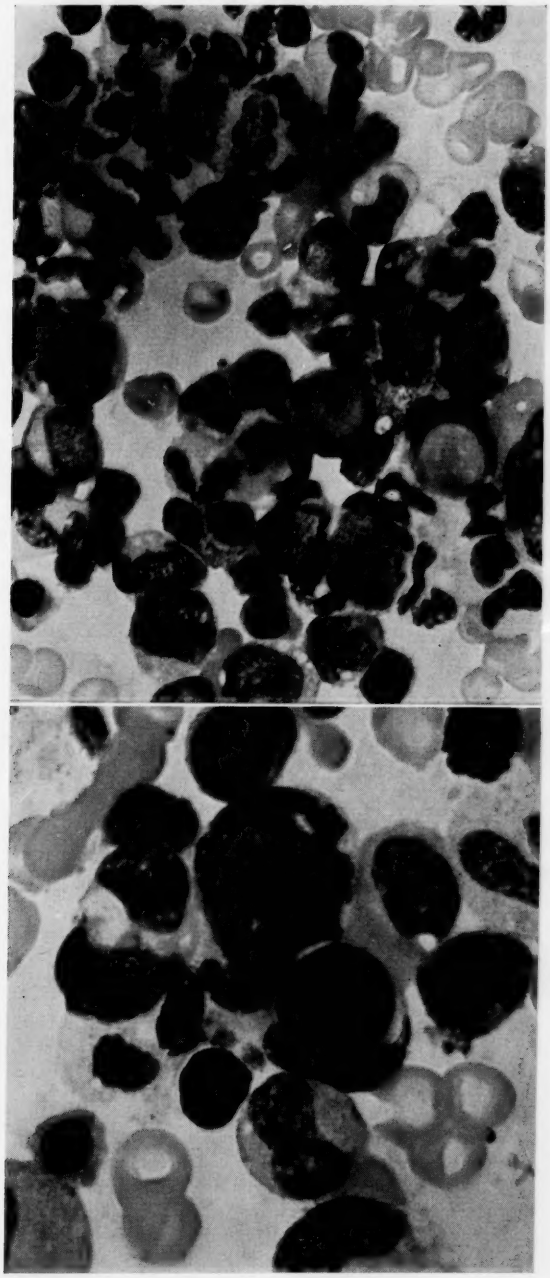
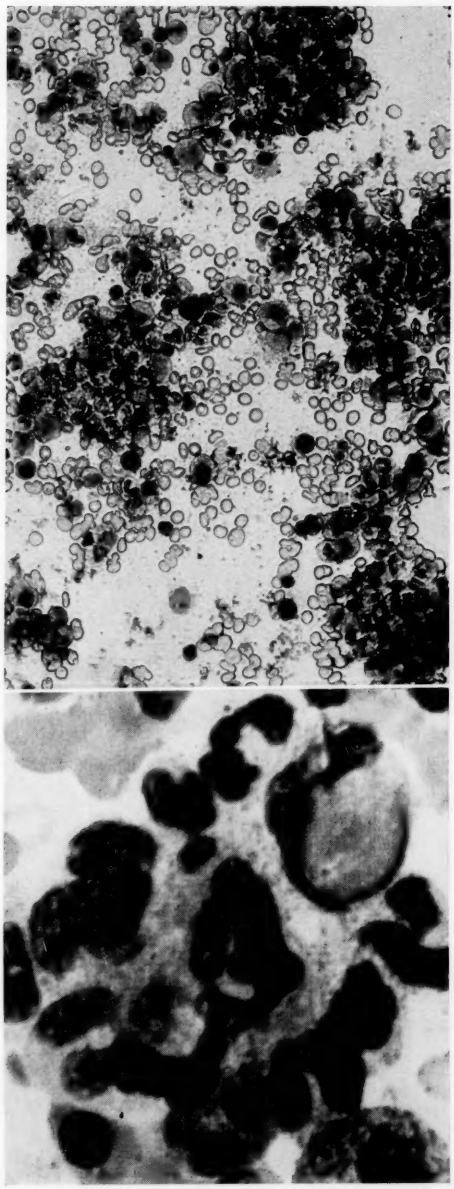
A.



B.

Fig. 1.—Bone marrow preparations in patients with S.L.E. *A-B*, L.E. cells and nucleophagocytosis; *A*, ×1,000; *B*, ×1,900. *C-D*, Rosette formation; *C*, ×300; *D*, ×1,900. *E-F*, Sections showing free hyaline bodies; *E*, ×500; *F*, ×1,000.

C.



D.

Fig. 1 (Cont'd).—For legend see page 597.

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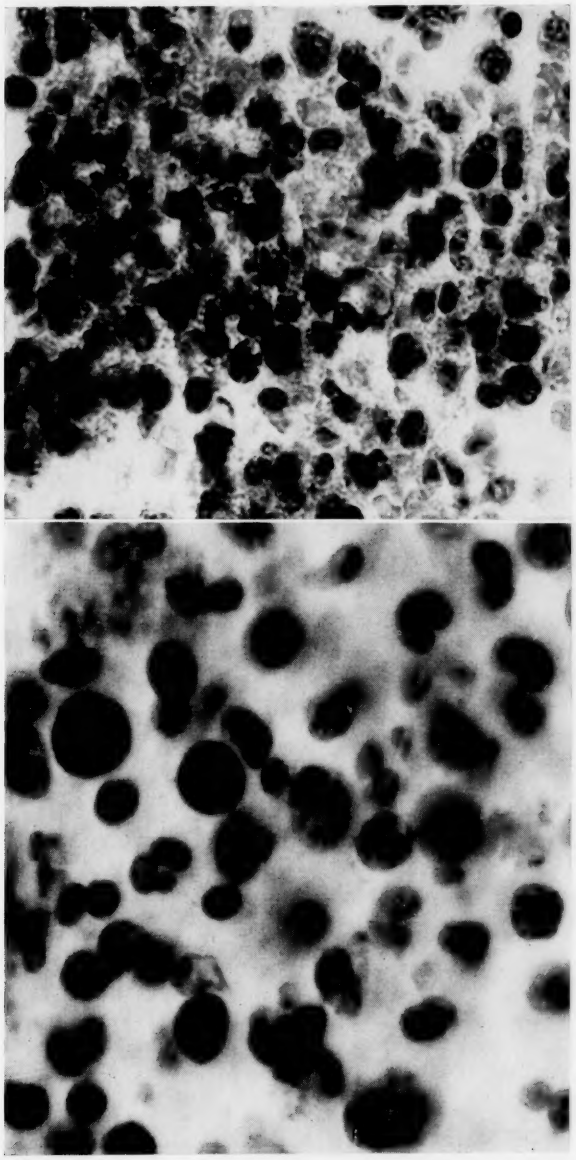
finding L.E. cells was remote. L.E. cells (Fig. 1, *A*, *B*) were more frequently seen than rosettes (Fig. 1, *C*, *D*). In some preparations from patients with proved S.L.E. only extracellular amorphous masses (Fig. 1, *E*, *F*) were found. These

E.



F.

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occurred either before or after the occurrence of a positive preparation. This finding has been observed by Suksta and Conley.[4] The presence of these masses is considered part of the L.E. phenomenon. This was seen in 4 per cent of the S.L.E. marrow preparations and 5 per cent of the blood preparations. Such preparations are reported from this laboratory as suspicious for systemic lupus erythematosus. For the purposes of this report, however, such tests were tabulated as negative. Leukophagocytosis and erythrophagocytosis were seen more frequently in preparations from patients with S.L.E. than with other diseases. Incubated marrow preparations from patients with acute infectious disease had free hyaline masses and leukoerythrophagocytosis more frequently than did other non-L.E. preparations. The free hyaline masses (Fig. 2, *E*, *F*), unlike those of S.L.E., retain their chromatin pattern and eosinophilic staining characteristics. This finding also has been reported by Hargraves.[5] In addition, the frequency and degree of phagocytosis and free masses were not as great as in S.L.E.

L.E. cells were found only in incubated marrow or blood preparations and were not observed in nonincubated blood or marrow specimens.

Cases of S.L.E.—The hospital records of 87 patients with S.L.E. were reviewed. The clinical and laboratory findings present at the time L.E. tests were performed are tabulated and correlated with the frequency of positive preparations. In some patients all the laboratory tests to be correlated were not performed at the time the L.E. test were obtained. This reduced the number of tests which could be correlated.

There were 71 women and 16 men. Four women patients were Negro. The mean age of onset was 25.6 years (standard deviation ± 8.3 years). Prior to the diagnosis of S.L.E. there were 12 patients (14.5 per cent) with symptoms attributed to rheumatoid arthritis for 3 to 12 years' duration; 2 (2.5 per cent) with chronic discoid lupus erythematosus; 1 patient with Sjogren's syndrome; 1 patient with Raynaud's disease; and 1 patient with seborrheic eczema (Table I). In reviewing the records of the patients of this series, reference to a history of drug reactions prior to the development of S.L.E. findings was not found. Two patients developed penicillin reactions after the onset of their L.E. symptoms. The most common initial symptoms (Table II) were: facial rash, 28 patients (36 per cent); various degrees of arthropathy, 24 patients (29 per cent);

TABLE I. DIAGNOSIS PRIOR TO ONSET OF S.L.E.

Rheumatoid arthritis	12
Chronic discoid L.E.	2
Sjogren's syndrome	1
Raynaud's disease	1
Idiopathic thrombocytopenic purpura	1
Dermatomyositis	1
Seborrhoic dermatitis	1
Skin allergy	1
Total number of patients	20

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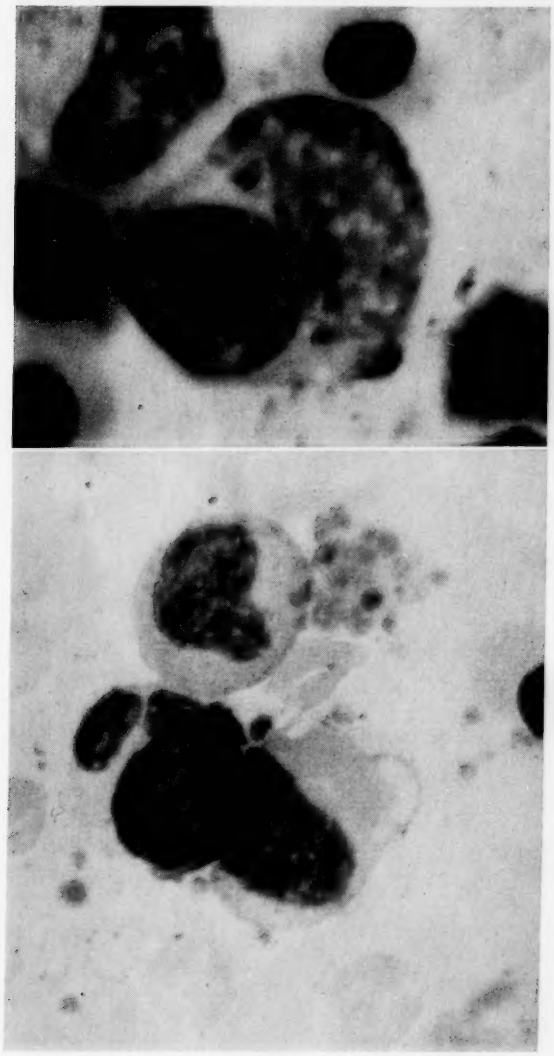
A.

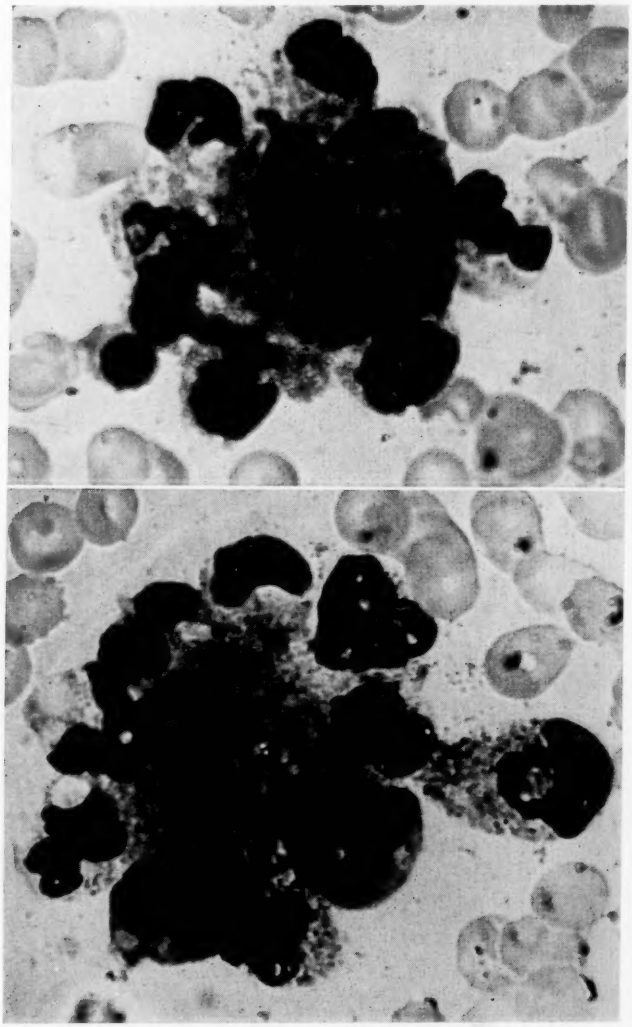


B.

Fig. 2.—Incubated bone marrow smear preparations in non-S.L.E. patients. *A*, Nucleophagocytosis by monocyte, ×3,100. *B*, Nucleophagocytosis by segmented neutrophil, ×2,100. *C*, Pseudo-rosette; clumping of marrow elements around megakaryocyte, ×1,600. *D*, Pseudo-rosette; clumping of granulocytes around megakaryocyte cytoplasm, ×1,600. *E*, Free hyalinized nucleus; pseudo-amorphous bodies, ×1,400. *F*, Free hyalinized nucleus; pseudo-amorphous body. Hyalinization approaches the homogeneous character of the amorphous masses found in S.L.E., ×1,500. *G*, Pseudo-L.E. cell. This structure appears to be a free hyalinized nucleus in which the margin has become folded or the chromatin has precipitated in such a manner to be suggestive of the eccentrically displaced nucleus of a phagocytizing cell, ×1,500.

arthropathy with fever, 6 patients (7 per cent); and facial rash with fever, 5 patients (6 per cent). The most common initial laboratory findings were anemia (< 12 Gm./100 ml. hemoglobin), hyperglobulinemia (> 3.0 Gm. per cent), proteinuria, and elevated sedimentation rate.

C.

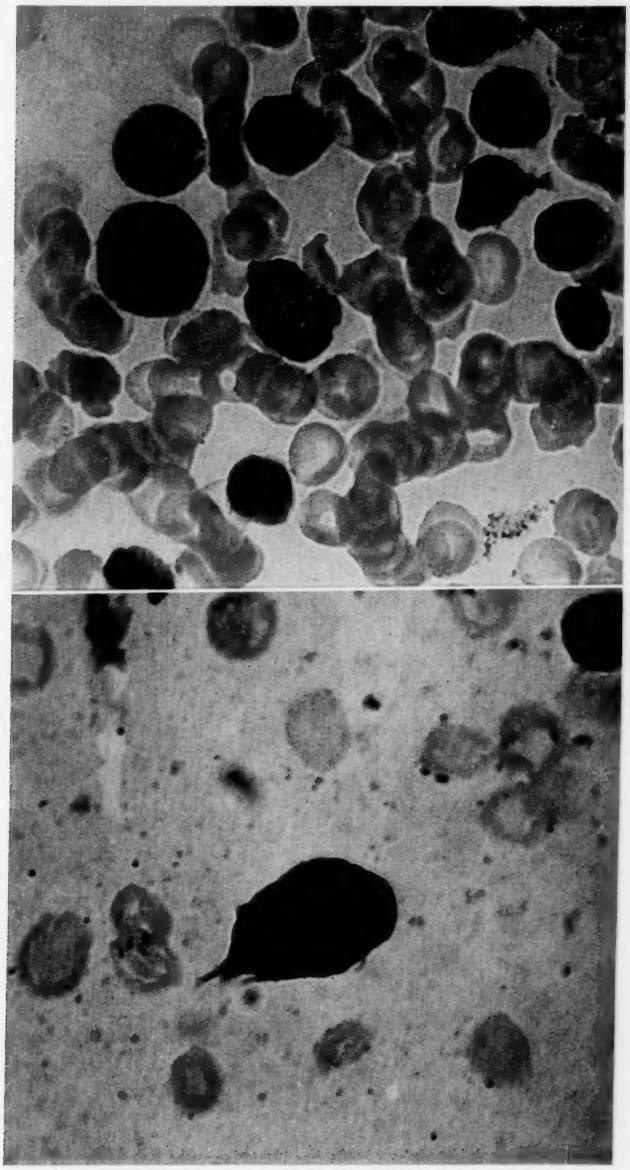


D.

Fig. 2 (Cont'd).—For legend see page 601.

The average duration of symptoms before the performance of the first L.E. test was 19.0 months; range 2 weeks to 10 years (standard deviation ± 2.4 years). However, the average duration of symptoms before the first positive L.E. test

E.



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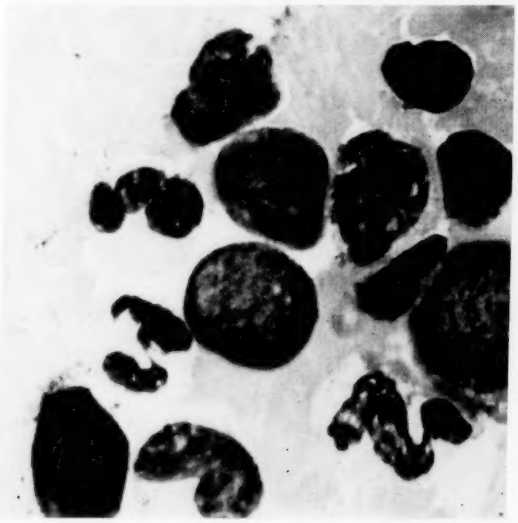
was 20.3 months; range 2 weeks to 14 years (standard deviation ± 2.9 years). The mean duration of life from onset of symptoms to death was 31.8 months; range 3 weeks to 12 years (standard deviation ± 2.4 years). Most of the preparations were thus obtained during the latter half of the illness. No significant correlation could be found between the duration of symptoms or duration of life and the frequency with which the L.E. test was positive. The diagnosis of S.L.E. was established by clinical, laboratory, and biopsy procedures.



G.

Fig. 2 (Cont'd).—For legend see page 601.

TABLE II. FREQUENCY OF INITIAL SYMPTOMS OF S.L.E. IN 77 PATIENTS

Facial rash	28
Arthropathy	24
Arthropathy and fever	6
Facial rash and fever	5
Pleurisy	3
Vasomotor symptoms	3
Abdominal enlargement	2
Abdominal pain	1
Fever	1
Arthropathy, fever, facial rash	1
Purpura	1
Anemia	1
Sjogren's syndrome	1
Total number of patients	77

In 45 patients the characteristic histologic changes of S.L.E. were demonstrated. Ante-mortem biopsies in 27 were positive (9 kidney, 14 skin, and 4 both skin and kidney biopsies). The characteristic lesions of S.L.E. were demonstrated on post-mortem examination in 18 patients.

In 42 patients, the diagnosis was established by clinical and laboratory abnormalities thought to be characteristic for S.L.E. Five patients in this group had normal biopsies (2 kidney, 2 skin, and 1 both skin and kidney). Positive biopsy findings have been obtained in 30 of these patients since completion of this study. Follow-up studies were not complete in 7 patients. Twelve of these patients were followed for less than 2 years.

Twenty-three patients are living and actively followed in the clinics. Twenty-seven patients have died. Necropsies were not performed in 7. The autopsy evidence for S.L.E. was not conclusive in 2 patients. The following is a short resumé of the pathologic findings in these patients:

H.B. was a 33-year-old white woman who died 10 years after the onset of migratory arthropathy. The only L.E. test (marrow preparation) was considered questionably positive, since an occasional rosette was found. L.E. cells were, however, not present. The patient died from Pseudomonas septicemia. Grossly, superficial ulcers of the mucosa of the gall bladder and gastrointestinal tract were found. The blood vessels of the heart, liver, muscles, and skin contained round cell infiltration in the perivascular area, adventitia, and propia. Some of the blood vessels had fibrotic lamellar thickening of their adventitia. Other vessels contained degenerative changes in the adventitia and propia. The walls of the small vessels in the spleen were slightly thickened, resembling an "onion skin." The glomerular basement membrane in the kidney was thickened. It was not certain whether these pathologic changes were more in keeping with lupus erythematosus or with periarteritis nodosa.

H.M. was a 26-year-old Negro woman who died 2 years after the onset of intermittent episodes of fever and migratory arthropathy. Terminally she developed occlusion of the blood vessels in her digits resulting in gangrene. In addition she had a false-positive serologic test for syphilis. Three L.E. preparations of her blood were negative, and one of the bone marrow was positive. The autopsy findings were referable mainly to the blood vessels. The arteries of the heart had monocytic perivascular infiltration, with either intimal thickening or perivascular fibrosis. The walls of the central arteries in the spleen had irregular thickening and laminated fibrosis of the adventitia. The small vessels of the spleen, gastrointestinal tract, and kidneys had minimal perivascular infiltration with mononuclear cells. Some of the blood vessel walls were fragmented while others contained thrombi. Aneurysmal dilation of some of the larger blood vessels was also found. The basement membrane in some of the glomeruli was thickened, while in other nephrons the tubules were dilated and contained hyaline material. Necrosis and inflammatory cell infiltration were also present in other renal areas. Though the pathologist concluded that these findings were more in keeping with periarteritis nodosa, the likelihood of lupus erythematosus could not be eliminated.

RESULTS

Occurrence of Positive L.E. Tests in Cases of S.L.E.—In 12 patients the diagnosis of S.L.E. was established only on clinical examination and laboratory findings. Long-term follow-up and biopsy procedures were not completed at the conclusion of this study. In 6 patients five marrow and nine blood L.E. tests were negative.

The largest portion of the series consisted of 75 patients in whom the diagnosis of L.E. was established by histologic criteria and/or the characteristic clinical course and abnormal laboratory findings. There were 116 bone marrow and 96 peripheral blood L.E. tests. L.E. cells with or without rosette formation were found in 72 bone marrow preparations (62 per cent) and 50 peripheral blood preparations (53 per cent).

Blood and bone marrow preparations were obtained within a 24-hour interval on 45 patients (Table III). Nineteen had more than one blood L.E. preparation and 10 patients had more than one bone marrow L.E. preparation. A negative bone marrow test was found in each of 6 patients with positive blood tests. Negative blood tests were found in 6 other patients who had positive marrow preparations. Neither the blood nor the bone marrow was positive in 8 other patients.

TABLE III. CORRELATION BETWEEN BLOOD AND MARROW PREPARATIONS OBTAINED WITHIN CLOSE INTERVALS IN PATIENTS WITH S.L.E.

L.E. TESTS		NO. PATIENTS	L.E. TESTS					
			PERIPHERAL BLOOD			BONE MARROW		
BLOOD	BONE MARROW		NO. OF PREPS.	NO. POS.	% POS.	NO. OF PREPS.	NO. POS.	% POS.
+	−	6	10	7		6	0	
−	+	6	9	0		9	7	
−	−	8	9	0		9	0	
+	+	25	38	32		31	26	
Total		45	66	39	59	55	33	60

The remaining 25 patients (67 per cent) each had positive blood and bone marrow preparations. There were 32 out of 38 (84 per cent) positive blood and 26 out of 31 (83 per cent) positive marrow preparations. In all four groups, half of the patients had tests performed more than once but not more than twice. The frequency with which tests were repeated in each group was similar, and did not appear to account for the group differences.

Twenty-seven patients did not have blood and bone marrow preparations obtained at or near the same time. In ten of these patients with negative marrow preparations (5 having only one test), each had one positive peripheral blood test. In 10 other patients in this group with negative peripheral blood preparations (9 had two tests each), each had a positive bone marrow test.

Positive blood or marrow tests were not obtained in 7 of these patients. In this group, however, only 1 patient had more than one blood test and 4 more than one marrow test.

In 1 patient daily blood L.E. preparations were obtained for a 2-week interval. One out of the 14 preparations was positive. One preparation was considered suspicious because of an increased number of amorphous masses.

Both initial blood and marrow preparations were negative in 10 of these patients (12.2 per cent). L.E. tests in these patients were subsequently positive.

TABLE IV. FREQUENCY OF POSITIVE L.E. PREPARATIONS IN THE PRESENCE OF INDIVIDUAL SYMPTOMS IN 65 PATIENTS WITH S.L.E.

SIGNS AND SYMPTOMS	NO. PTS.	BONE MARROW		PERIPHERAL BLOOD	
		NO. + TESTS	% + TESTS	NO. + TESTS	% + TESTS
Rash	46	22	62	26	58
Joints	44	45	64	32	47
Fever	48	44	63	26	46
Anemia	53	43	59	24	44
Leukopenia	13	12	75	6	75
↑ Csr	58	52	63	39	49
Adenopathy	19	15	21	8	50
Spleen ↑	13	8	53	7	53
Liver ↑	23	8	44	14	61
Ceph. Floc. ↑	23	19	64	9	33
Thymol Turb. ↑	24	18	72	11	42
Ser-bilirubin ↑	10	5	42	6	50
Globulin ↑	46	39	63	35	54
Albumin ↓	38	32	63	25	53
Albuminuria	41	37	77	18	42
Urinary casts	21	16	84	21	30
Hematuria	20	18	91	11	42
Pleural effusion	12	10	91	6	46
Pleuritis	18	12	67	10	62
Cough	14	9	64	4	40
Pneumonia	12	10	71	5	50
Pericarditis	7	5	84	3	33
Heart Failure	5	6	100	2	50
Pericardial effusion	4	3	100	2	67
Edema	11	9	69	2	28
Anorexia	11	8	53	3	60
Nausea or vomiting	10	6	46	2	50
Weight loss	17	12	55	12	48
Diarrhea	3	8	89	0	0
Cap. Frag. ↑	4	2	67	4	63
Purpura	7	3	43	4	26
Prothrombin time ↑	2	2	100	1	20
Epistaxis	3	3	75	3	100
Serology +	5	5	72	2	40
Cryoglobulin	3	2	67	0	0
Coombs' test +	7	6	67	0	0
Neuropathy	3	3	75	3	60
Psychiatric abnormality	7	3	50	5	62
Convulsions	5	4	100	1	50
Vascular occlusion	3	1	100	0	0
Vaso-Inst.	8	5	83	9	60
Kidney biopsy +	15	10	77	5	38
Skin biopsy +	18	5	33	2	29

↑ = increase.
+ = positive.

Correlation Between the Clinical-laboratory Abnormalities of S.L.E. and the L.E. Test:—Analysis was performed of the frequency with which positive L.E. tests occurred in the presence or absence of various clinical and laboratory abnormalities of S.L.E. The results from 65 patients are found in Table IV. In general, significant correlation could not be found between the frequency of positive L.E. tests in blood or marrow preparations and single clinical and labora-

tory features of S.L.E. Neither marrow nor peripheral blood tests correlated with kidney or skin biopsy findings. Out of 76 patients, 15 had 33 percutaneous renal biopsies,[6] 18 (54.5 per cent) had renal changes consistent with L.E. Twenty patients had 26 skin biopsies of L.E.-like skin lesions; 20 (77 per cent) had histologic changes characteristic of L.E. Positive biopsy specimens from the skin or kidney did not appear to be significantly more frequent than positive L.E. tests.

More than three-fourths of the marrow preparations were positive in patients with marked renal, cardiovascular, or neurologic involvement. In patients with leukopenia 75 per cent of the blood tests were positive.

Correlations between different combinations of clinical-laboratory abnormalities and L.E. tests were also performed (See Table V). Correlation was found between marrow tests and those groups made up of different combinations of arthropathy, rash, fever, urinary findings, and abnormal liver function tests (thymol turbidity, cephalin flocculation, and/or A/G ratio). The best correlation occurred whenever arthropathy and rash were included in the group to be correlated. In general, better correlations were found in groups with two or more abnormal findings. The percentage of positive tests was also somewhat greater when more findings were present. Marrow tests seemed to correlate more frequently (8 out of 21) than blood tests (2 out of 21). The tendency to find a larger number of positive tests in those groups with more than one abnormality would support the clinical impression that L.E. tests are more frequently positive when the illness affects many body systems.

TABLE V. CORRELATION OF VARIOUS GROUPS OF FINDINGS IN S.L.E. AND L.E. TEST

CLINICAL FINDINGS	NO. PTS.	BONE MARROW		PERIPHERAL BLOOD	
		NO. + TESTS	% + TESTS	NO. + TESTS	% + TESTS
Joint, rash	28	30	83	19	68
Joint, rash, fever	24	22	76	14	48
Joint, rash, fever, albuminuria, casts	9	10	91	6	43
Joint, fever, rash, albuminuria, casts, rbc	7	9	100	4	36
Joints, rash, ± fever, pulmonary disease	18	16	76	12	63
Joints, rash, ± fever, cardiac disease	9	10	82	4	50
Joints, rash, ± fever, neurologic disease	8	8	80	9	69
Joint, rash, ± fever, leukopenia	11	11	72	6	75
Joint, rash, ± fever, serology	2	2	—	1	—
Joint, rash, ± fever, albuminuria	—	15	88	14	58
Joint, rash, fever, thymol turb., ceph., globulin	4	3	75	4	67
Joints, rash, fever, thymol turb., ceph., A/G rev., albuminuria	4	3	75	5	83
Joints, fever, albuminuria	28	30	71	18	42
Joints, albuminuria, anemia	27	28	72	18	44
Joints, albuminuria, anemia, splenomegaly	5	5	100	3	32
Joints, albuminuria, anemia, hepatomegaly	9	9	90	7	54
Rash, albuminuria, anemia	19	14	74	12	50
Rash, albuminuria	23	20	95	13	46
Coombs' +, anemia	9	9	75	8	80
Thymol turb., ceph. floc.	17	14	74	7	39
Thymol turb., ceph. floc. A/G	16	13	64	5	36

The percentage of positive marrow tests was lower during therapy, but not significantly so.

The L.E. Test in Subacute and Chronic Discoid Lupus Erythematosus.—There were 9 patients with chronic discoid lupus erythematosus. Ages ranged from 24 to 57 years. Two were men. Three patients each had one blood preparation. Seven patients each had one bone marrow preparation. All tests were negative.

There were 9 patients with subacute lupus erythematosus. Three were males. One marrow test was performed on 7 of these patients; in 2 a blood preparation was also made. All of the tests were negative.

L.E. Tests in Other Diseases.—L.E. tests were performed in 343 patients with different diseases (Table VI). There were 238 bone marrow preparations and 214 peripheral blood preparations; all were negative. In 66 patients, both blood and marrow preparations were obtained. Only 11 patients had more than one blood preparation, and 7 had more than one marrow preparation. There were 10 patients with drug reactions (4 penicillin, 3 hydralazine, 1 sulfadiazine, 1 quinidine, and 1 streptomycin) in whom 5 bone marrow and eight peripheral

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TABLE VI. THE L.E. TEST IN OTHER DISEASES

DISEASE	NO. PTS.	AGE RANGE	NO. NEGRO	NO. MALES	BONE MARROW	PERIPHERAL BLOOD
Rheumatoid arthritis	51	6–49	10	11	23	57
Rheumatic fever	6	4–41	3	1	4	7
Glomerulonephritis	14	4–63	6	4	8	12
Nephrotic syndrome	3	20–36	1	2	3	4
Erythema multiforme	1	36	0	0	1	0
Scleroderma	3	36–57	1	2	0	3
Dermatomyositis	1	72	1	0	0	1
Eczema	3	23	0	1	3	1
Neurosis	11	19–66	1	4	8	9
Penicillin reaction	4	34–56	1	3	2	4
Apresoline reaction	3	45–56	0	3	2	2
Sulfa reaction	1	45	0	1	0	1
Allergic drug eruption	4	16–50	0	4	5	4
Iron deficiency anemia	12	29–66	0	2	9	5
Aplastic anemia	5	12–65	2	2	2	5
Hereditary hemolytic anemias	3	17–43	1	1	2	1
Acquired hemolytic anemias	6	13–63	1	3	5	4
Polycythemia vera	2	29–66	0	1	1	2
Adenopathy	5	13–50	1	0	3	3
Splenomegaly	4	8–31	0	0	3	2
Pancytopenia	3	50–64	0	0	2	1
Myeloid metaplasia	2	60–72	0	1	1	1
Chronic lymphocytic leukemia	1	66	0	1	0	1
Chronic granulocytic leukemia	2	44–56	0	0	1	2
Acute leukemia	1	14	0	0	0	1
Lymphosarcoma	10	25–69	0	5	6	9
Hodgkin's disease	5	31–58	0	2	4	3
Thrombocytopenic purpura	15	3–49	0	4	11	10
Nonthrombocytopenic purpura	11	23–56	1	0	7	9
Visceral bleeding	11	12–45	1	0	6	10
Hypothyroidism	3	31–41	1	0	1	6
Fever of unknown origin	12	5–60	1	4	4	15
Miscellaneous	28	11–69	4	6	12	21

blood L.E. tests were obtained. In 79 patients with different forms of collagen disease there were 39 bone marrow and 84 peripheral blood tests. In 51 patients with rheumatoid arthritis, 80 L.E. tests were performed (23 bone marrow and 57 peripheral blood preparations). L.E. tests were obtained after discontinuation of steroid in 10 of these patients.

L.E. preparations are performed routinely on all patients with idiopathic thrombocytopenic purpura, since this disorder has been reported to precede the onset of clinical S.L.E.[7,8] In 15 patients all 11 bone marrow and 10 blood preparations were negative. In 1 patient, a 36-year-old white woman, thrombocytopenic purpura occurred 5 years before the onset of symptoms attributed to S.L.E. The platelet count became normal following splenectomy. L.E. preparations were not obtained at the time of the thrombocytopenia. The spleen sections were reported as normal; however, 5 years later, after the onset of L.E., the sections were reviewed and vascular changes of S.L.E. were found. Eleven patients with purpura due to vascular defects, Henoch-Schoenlein type, had 7 bone marrow and 9 peripheral blood preparations. All were negative.

There were 6 patients with idiopathic acquired hemolytic anemia who had 5 bone marrow and 4 blood preparations. No L.E. cells or rosettes were found in any of the preparations. In 31 patients having fever of unknown origin, unexplained splenomegaly, or other general manifestations, a definitive explanation for their symptomatology could not be found after extensive laboratory investigation. All 18 bone marrow and 26 peripheral blood preparations were negative. To our knowledge none of these patients have developed definitive findings of S.L.E.

During the past 3 years we have performed approximately 285 bone marrow and 465 peripheral blood preparations in 500 patients. To date, false-positive L.E. tests have not been observed.

DISCUSSION

False-Positive L.E. Tests.—Cells resembling L.E. cells have been reported in various drug reactions: penicillin,[8-11] hydralazine,[13-16] tetanus antitoxin, hydantoin,[12] and in eczematoid reactions from sulfonamides, iodine, thiouracil, arsphenamine, buthethol, and Peruvial balsam.[17] Of the original four reports on hydralazine hypersensitivity, only Shackman, Swiller, and Morrison[13] presented photomicrographs of the cells observed. One of the cells shown was crushed, thereby rendering morphologic delineation difficult. In a recent report by Weiss and Swift,[18] photomicrographs are shown of L.E. cells observed in patients with hydralazine hypersensitivity. They were also able to produce rosettelike formation by the addition of buffered hydralazine to the blood buffy layer in vitro. Apparently the L.E.-like hydralazine hypersensitivity syndrome seen in humans has been produced in dogs by Comens.[17] The ability of hydralazine to induce an L.E. state seems well documented and apparently confirmed by laboratory experiments. The occurrence of the L.E. cell in such states should not be regarded as false-positive tests since all of the patients reported have also developed symptoms resembling S.L.E.

Since the report of Walsh and Zimmerman[9] on the occurrence of L.E.-like cells in 3 patients with penicillin hypersensitivity, three additional reports[9-11] have described similar findings. Dubois[19] was of the opinion that 2 of the 3 patients reported by Walsh and Zimmerman[9] had abnormal urinary sediments and other changes usually found in S.L.E. According to Jacobs,[11] the other patient "continues to have a picture that may be related to systemic lupus erythematosus." There appears to be some question of the identity of the L.E. cells shown in Paull's[10] report of a patient with severe penicillin hypersensitivity. Miescher and DeLacretaz[12] performed L.E. tests on the blood of 3 patients with penicillin reaction. In 1 patient with severe erythroderma associated with penicillin reaction, 18 L.E. cells were found. The L.E. cell shown did not appear to be a typical cell. Jacobs[11] reported 1 patient with miliary tuberculosis in whom L.E. cells were found 2 months after a purpuric eczematoid reaction from oral penicillin. The patient died 59 days after the onset of the reaction. The only lesions found at autopsy were histologic changes attributed to miliary tuberculosis. The symptoms which are associated with penicillin reaction disappear within 4 weeks after their onset. In only 1 patient[7] were L.E. cells present 9 weeks after the onset of the reaction. The prolonged symptoms of Jacobs'[11] patient makes one suspect her symptoms were either attributed to the miliary tuberculosis or to S.L.E. which could not be demonstrated at autopsy.

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Unlike hydralazine, penicillin hypersensitivity syndromes with L.E. cells have not been reproduced in animals. Hargraves,[5] Conley,[20] Dubois,[19,21] Haserick,[22] Weiss and Swift,[18] and Ross and Wells[23] have not found L.E. cells in patients with penicillin hypersensitivity. The evidence seems to indicate that if penicillin L.E.-like syndromes can be produced they are extremely rare. On the other hand, the rare occurrence of this syndrome attracts the suspicion that such patients may have subclinical S.L.E. prior to penicillin administration. Careful follow-up of patients with this problem may support this possibility.

L.E. cells have been reported in other diseases. Slocumb[24] and Hargraves[5] have found L.E. cells in patients with rheumatoid arthritis following the withdrawal of cortisone therapy. L.E. cells were also found in 5 out of 46 patients with rheumatoid arthritis by Weiss and Swift.[18] In patients with rheumatoid arthritis, Harvey in 116 patients and we in 51 were unable to find any L.E. cells. The relationship between S.L.E. and rheumatoid arthritis is not clear since one may mimic the other. Whether these patients had the rheumatoid picture of S.L.E. or false positive tests will require further investigation.

Nucleophagocytosis.—The morphologic differentiation between nucleophagocytosis (tart cell) (Fig. 2, *A*) and the L.E. cell is of primary importance in the evaluation of an L.E. preparation. The significance of nucleophagocytosis and its relationship to leukophagocytosis is not well understood. However, we believe the significance of nucleophagocytosis has been overstressed and that this phenomenon bears little significance in the diagnosis of lupus erythematosus. In a recent paper by Holman and Kunkel,[18a] Friou has shown the serum L.E. factor to be a γ globulin which appears to react with antiserum to normal γ globulin. They stated that this was suggestive that the factor was an antibody, possibly an autoantibody, to nucleoprotein or deoxyribonucleic acid. Several re-

ports have stressed the increased amount of nucleophagocytosis found in S.L.E. and various hypersensitivity reactions. Occasionally L.E. smears are reported as: "Increased nucleophagocytosis was found but no definite L.E. cells were seen." Such statements imply a relationship between the two phenomena.* We have observed leukophagocytosis and nucleophagocytosis, however, in many diseases, particularly in incubated marrows from children with acute infectious disease. Nucleophagocytosis may often be observed in vivo, whereas we have not found the L.E. phenomenon in vivo. It has been our observation that the amount of free hyaline bodies, and leukocyte and nuclear phagocytosis, is influenced by the degree to which specimens are agitated in preparation, the cleanliness of the equipment used, and the duration and temperature of the incubation. Leukocytes degenerate, and their nuclei hyalinize when incubated for longer than 3 hours. These nuclear masses occasionally resemble the basket cell seen in chronic lymphocytic leukemia. Factors which decrease the life span of the cells appear to increase the amount of nucleophagocytosis and number of hyaline cells. Whether the ingested nuclear mass is intact or hyalinized has not been shown to be of diagnostic or prognostic importance. Hyalinization may well be related to the length of time a cell has been dead.

Increased numbers of hyalinized nuclear masses are often found at the fibrinated edge of the smear (Fig. 2, *E*, *F*). Occasionally such a mass becomes spread out and a portion of its edge folded upon itself, staining darker than the remainder of the mass. To the inexperienced eye, under low magnification, such masses may resemble L.E. cells (Fig. 2, *G*). The accumulation of leukocytes around such masses may also simulate rosette formation (Fig. 2, *C*, *D*). Careful examination will reveal their chromatin structure. Many artifacts are found in L.E. smears, especially when performed by inexperienced persons. Usually the cell concentration is either too sparse or so thick that the morphology of cells becomes obscure. The preparation of the specimen is, therefore, important in the interpretation.

Hargraves[5] uses the term "tart cell" synonymously with nucleophagocytosis. This phagocytosis is accomplished by large reticuloendothelial cells and "also by neutrophils, monocytes, and small histiocytes." We would favor this concept for the sake of avoiding further confusion. There seems to be little reason to classify further necleophagocytosis according to the type of phagocytic cells or the degree of hyalinization of the ingested mass. However, we would agree that occasionally the degree of hyalinization of the phagocytized body may obliterate its chromatin structure so that differentiating it from an L.E. cell may be difficult. In addition, it is not always possible to identify the phagocytic cell. If the morphologic criteria of the L.E. cell as described by Hargraves[5] are strictly adhered to, the question of false-positive tests rarely arises.

The L.E. Test in S.L.E.—The frequency with which L.E. cells are found in patients in whom the diagnosis of S.L.E. was made varies in different reports. In this series 85 per cent of the patients had positive tests. Dubois[19] found

*Many of the preparations from patients in this series appeared to have a greater incidence of nucleophagocytosis.

positive tests in 70 to 80 per cent of the patients he reported. Haserick[22] surveyed the opinions of 20 hematologists from each section of this country. The frequency of false-negative tests varied with each hematologist, from rare to as high as 40 per cent. These figures apparently refer to the percentage of patients with S.L.E. who did not have positive tests.

False negative tests occurred at some time during the course of the disease in 50 per cent of the patients in this series. It appears that false-negative tests occur during some phases of the disease in all patients with S.L.E. In some patients with classic S.L.E., tests may have to be repeated several times before obtaining positive results. Dubois[19] stated: ". . . tests may be negative in patients with classic S.L.E. for years or throughout the entire course of their illness." Positive L.E. tests were never found in 15 per cent of the patients in this series. Each patient, however, received an average of 2.2 tests. Positive tests may have been obtained had a larger number of tests been performed.

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The frequency with which random L.E. tests are positive in S.L.E. is not well documented. Weiss and Swift[18] reported 38 per cent of the tests were positive in their patients with S.L.E. Most investigators[5,19,22] report the number of positive tests in relation to the number of patients rather than to the number of tests performed. This, however, gives a false sense of perspective when applying the L.E. test as a diagnostic tool. Through 85 per cent of the patients in this series with S.L.E. had positive tests, only 62 per cent of the marrow and 53 per cent of the peripheral blood tests were positive. This point is emphasized since we have repeatedly noted some physicians reassured of the absence of S.L.E. when tests are reported negative. This misconception is further amplified by the frequent request for L.E. tests to "rule out" S.L.E. The frequency with which positive results were obtained from the L.E. test was not significantly different from those obtained from kidney or liver biopsy.

Harvey and associates[20] could not find any regular correlation between the occurrence of L.E. cells and some of the abnormal laboratory findings, although a high percentage of patients with L.E. cells displayed other serologic abnormalities. Significant correlation between individual symptoms and frequency of positive tests was not found in this series. Correlations between multiple symptom combinations and the L.E. test appeared more significant. This finding would be in keeping with statements in the literature which imply a relationship between the frequency of positive tests and the extent of the disease. The duration of symptoms, or duration of life, was not significantly related to the frequency of positive L.E. tests.

SUMMARY

1. Blood and bone marrow L.E. preparations were obtained in 87 patients with S.L.E.

2. There were 72 (62 per cent) positive marrow and 50 (53 per cent) positive peripheral blood L.E. preparations. A significant difference between the frequency of positive marrow and blood preparations was not found.

3. Correlations were higher between groups of abnormal findings and the L.E. test than between single abnormal findings and the L.E. test.

4. Positive L.E. tests were not observed in 9 patients with subacute lupus and 9 patients with chronic discoid lupus.

5. False-positive L.E. tests were not observed in 230 patients with disorders other than S.L.E., including rheumatoid arthritis and various drug reactions.

6. In our experience the L.E. test is specific for the S.L.E. syndrome.

7. The differentiation between non-L.E. nucleophagocytosis and L.E. nucleophagocytosis is discussed.

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EFFECT OF A PATIENT-CYCLED BREATHING AID ON VENTILATORY EFFICIENCY IN PULMONARY EMPHYSEMA AND POLIOMYELITIS

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THE purpose of this report is to describe the effects of a mechanical aid to breathing which has several unique effects: (1) alveolar ventilation is enhanced by increase of reserve volume respiration, and (2) the total minute volume of breathing is regulated by the individual patient's response to the more efficient ventilation provided. A minute-to-minute adjustment to the chemical requirements of respiration is accomplished by an automatic sensing device whereby the respiratory rate is controlled by means of a new type of mechanical breathing aid. At present, patients with varying metabolic needs are artificially ventilated with a fixed cycling rate and predetermined pressure; hypoventilation and, more frequently, hyperventilation frequently take place.[1] Our initial studies on the effects of the patient's respiratory center in the regulation of the minute volume of breathing, as well as the effects of this special method of mechanical ventilation are here presented.

The Pneumatic Breathing Aid (P.B.A.) is an apparatus recently developed in our clinic by which the respiratory rate is regulated by the response of the respiratory centers to the patient's own arterial pCO_2, pH and pO_2, the tidal volume being determined by the degree and duration of pressure applied. The effects of pressure exerted on the lateral chest wall by means of a pneumatic jacket will be described in cases with pulmonary emphysema and poliomyelitis.

APPARATUS AND METHODS

The pneumatic breathing aid operates in the following manner. A sensing device, by which the patient is connected to the accessory ventilatory system, is

activated by the transfer of a small volume of air from a tube placed beneath the patient's nostrils to either a thermistor activated by the differential temperature produced in a sensing unit or by the flow of air moving a vane across a photoelectric cell. During initiation of expiration an impulse is produced which is amplified by an electronic system and, by means of a relay, opens a valve permitting air under pressure from a motor-blower unit to enter two plastic jackets encircling the lower lateral chest wall. A peak air pressure of between 40 to 60 mm. Hg is exerted upon the lower chest wall for 2 to 4 seconds. A safety valve opens to the atmosphere when pressures within the jackets exceed 40 mm. Hg.

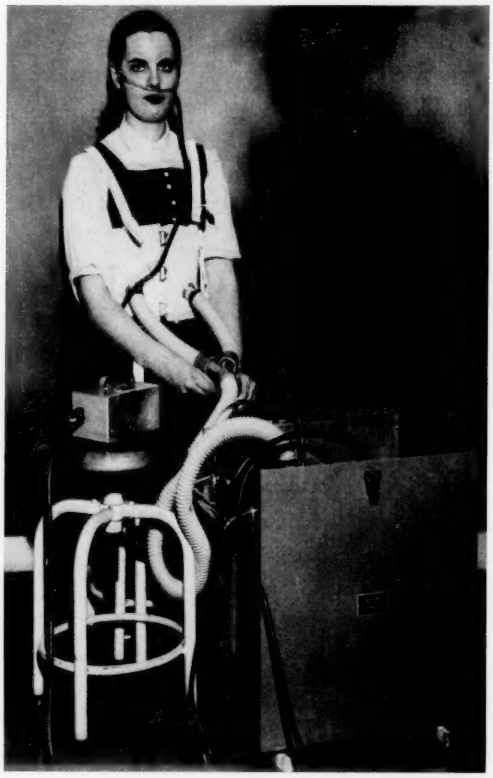

Fig. 1.

After completion of expiratory lower thoracic compression, which results in a variable increase in expiratory volume, the patient initiates the following inspiration as a result of the combined effect of impulses from the respiratory center, the carotid sinus, and reflexes originating from the lungs and moving framework of the chest wall. The patient's subsequent inspiration then takes place at a time and frequency determined by his own response to the increased gas diffusion which resulted from increased tidal and alveolar ventilation. Inflation of the lungs is achieved by the recoil of the thorax and active contraction of the inspiratory musculature of the patient. The apparatus is portable, as seen in the accompanying Fig. 1.

The pulmonary ventilation was recorded on a 9 liter spirometer. A previously described method of obtaining level respiratory graphs and simultaneous measurements of the oxygen consumption was utilized.[2*]

When the sensing device is in operation, the patient regulates the minute volume of breathing by selecting the respiratory rate suited to his varying metabolic needs. To increase the usefulness of P.B.A., provision has been made to change the triggering device from patient-controlled to automatic operation, transforming it into an inspiratory and expiratory time-regulated system. When operated on automatic cycling, expiratory lower rib compression can be achieved in apneic patients and also in hypoventilation states when the flow is too low to activate the sensing device, e.g., in patients with severe respiratory muscle impairment due to neuromuscular disease or respiratory depression associated with respiratory acidosis in advanced pulmonary emphysema.

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RESULTS

The physiologic and clinical effects of the application of P.B.A. for short periods were studied in a group of patients with pulmonary emphysema and poliomyelitis with dyspnea.

In the patients with poliomyelitis, an increase in tidal air volume resulting from expiratory compression of the lower chest wall, was accompanied by a concomitant increase in minute ventilation and a decrease in respiratory rate. These results are shown in Table I.

The shallow breathing of patients with poliomyelitis results in hypoventilation and is characteristically accompanied by hypoxia and retention of carbon dioxide. An increase in reserve volume respiration produced a more effective ventilation with immediate relief of the sensation of dyspnea. It was previously shown that manual compression of the chest wall was followed by relief of dyspnea in similar cases due to increase in tidal air as well as total minute volume of breathing[3]; it was concluded from this study that a device like P.B.A. would result in elevation of the pulmonary ventilation of a sufficient degree to relieve dyspnea without the hazard of alkalosis provided the rate of respiration could be selected by the patient and in that way the total minute volume would be regulated. Additional studies are required to determine the blood gas changes produced with patient-cycled apparatus, but it was clinically clear that dyspnea was relieved.

In patients with pulmonary emphysema summarized in Table II the tidal air increase was similarly accomplished by expiratory pressure on the lateral chest wall; the respiratory rate selected by the patient in all except 2 cases was lower than that which the patient manifested without the use of the pneumatic breathing aid. The pulmonary ventilation was, in 6 instances, the same or lower than that found when the patient was breathing spontaneously; in 10 other instances, it was elevated above the control value. Since increased alveolar

*The measurement of the blood gases reported here was performed in the laboratory of Dr. Alfred P. Fishman and is part of further studies now in progress.

TABLE I. EFFECT OF P.B.A. ON PULMONARY VENTILATION, TIDAL AIR, AND RESPIRATORY RATE IN 6 PATIENTS WITH POLIOMYELITIS

CASE NO.	PULMONARY VENTILATION C.C./MINUTE			TIDAL AIR C.C./BREATH			RESPIRATORY RATE RR/MINUTE		
	CONTROL	DURING P.B.A.	PER CENT CHANGE OVER CONTROL	CONTROL	DURING P.B.A.	PER CENT CHANGE OVER CONTROL	CONTROL	DURING P.B.A.	PER CENT CHANGE OVER CONTROL
1	5750	7000	+22	380	500	+32	15	14	−1
2	4600	5500	+20	270	390	+44	17	14	−3
3	4700	6000	+28	240	460	+92	20	13	−7
4	6400	6500	+2	320	500	+56	20	13	−7
5	3200	4900	+52	160	270	+69	20	18	−2
6	3500	4800	+37	180	600	+230	19	8	−11
Mean			+27			+87			−5

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TABLE II. EFFECT OF P.B.A. ON PULMONARY VENTILATION, TIDAL AIR, AND RESPIRATORY RATE IN 16 PATIENTS WITH PULMONARY EMPHYSEMA

CASE NO.	PULMONARY VENTILATION C.C./MINUTE			TIDAL AIR C.C./BREATH			RESPIRATORY RATE RR/MINUTE		
	CONTROL	DURING P.B.A.	PER CENT CHANGE OVER CONTROL	CONTROL	DURING P.B.A.	PER CENT CHANGE OVER CONTROL	CONTROL	DURING P.B.A.	PER CENT CHANGE OVER CONTROL
1	4860	5330	+10	490	670	+37	10	8	−2
2	9880	8540	−14	500	710	+43	20	12	−8
3	7730	8340	+ 8	600	830	+40	13	10	−3
4	6970	7720	+11	440	700	+59	16	11	−5
5	10370	10640	+ 3	790	1200	+52	13	9	−4
6	7350	8350	+14	410	760	+85	18	11	−7
7	5700	6490	+14	630	650	+ 3	9	10	+1
8	6400	7180	+12	380	550	+45	17	13	−4
9	5630	6630	+18	800	1100	+37	7	6	−1
10	12900	11600	−10	480	1450	+202	27	8	−19
11	7100	4860	−32	270	810	+200	26	6	−20
12	5480	5480	0	500	610	+22	11	9	−2
13	13300	11800	−11	890	910	+ 2	15	13	−2
14	7300	5800	−20	450	530	+18	16	11	−5
15	8800	12000	+36	680	1100	+47	13	11	−2
16	7100	7900	+11	370	490	+32	19	16	−3
Mean			+ 3			+23			−5

ventilation in emphysema may be assumed to take place as the result of the increased tidal air, a more efficient exchange of oxygen and carbon dioxide thus provided was responsible in 5 patients for selection of the lower minute volume of breathing. The difference in minute volume before and during application of P.B.A. revealing the increase in tidal air and decrease in respiratory rate are revealed in the spirograms obtained in a patient with poliomyelitis (Fig. 2).

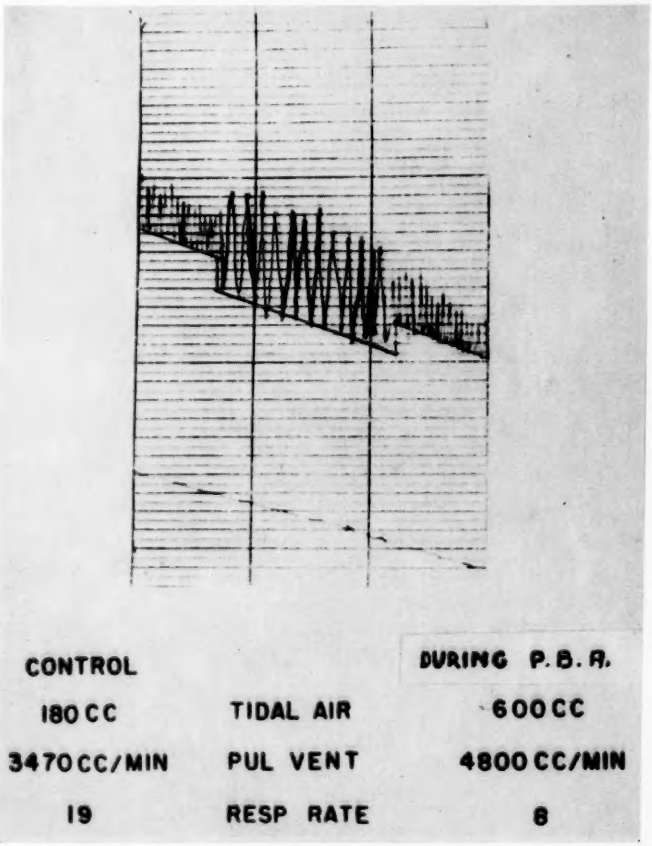

Fig. 2.—Increased minute volume of ventilation accomplished by P.B.A. as a result of increase in tidal air from 180 to 600 c.c. Patient-cycled apparatus to provide respiratory rate of 8 instead of 19 per minute, a result of increased efficiency of elevated reserve volume respiration.

In a patient with pulmonary emphysema, a similar reduction in pulmonary ventilation from 15.1 to 10.9 liters per minute was accompanied by a reduction in respiratory rate from 28 to 6. The tidal air increase was from 540 to 1820 c.c. (Fig. 3).

In a patient with severe pulmonary emphysema in whom the pneumatic breathing aid was employed over a period of one-half hour, a 20 per cent lowering of the volume of breathing was not associated with a significant change in the

blood gases or pH, as seen in Table III. It would appear that this patient "chose" to relieve dyspnea and to reduce the work of breathing by lowering his minute volume of ventilation, rather than to maintain the previous ventilation, which presumably would have resulted in restoration toward the normal of the arterial blood gases.*

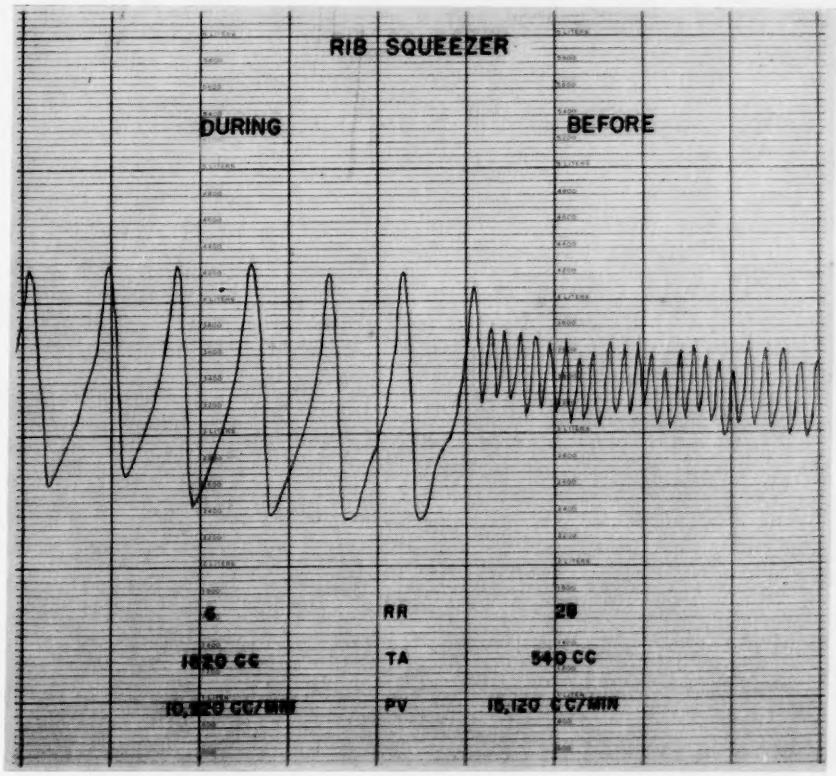

Fig. 3.—Decrease of respiratory rate from 28 to 6 occurred following increase of tidal air from 540 to 1,820 c.c.

Ventilatory studies carried out in patients with pulmonary emphysema while breathing air and 100 per cent oxygen have been used as a test of the degree of clinically observed respiratory insufficiency, i.e., dyspnea.[4,5] A series of 10 pa-

*The priority of the factors which determine the work of breathing over stimuli from the respiratory center has been indicated in various studies from our clinic, some of which have been summarized[9] and others are now in press; in patients with pulmonary emphysema the response to various therapeutic measures which decrease pulmonary effort is represented by a lowering of the minute volume of breathing without change in hypercapnea. The resultant decrease in CO_2 production is one of the beneficial consequences of homeostatic elevation of pCO_2 during oxygen therapy. In recent studies in which patients have breathed 32 per cent oxygen during walking exercise, by means of a pocket oxygen cylinder device (Oxy-Neb) the burdensome dyspnea was almost absent, as compared to similar exertion breathing air. The value of oxygen therapy during exercise confirms its value at rest.

The Oxy-Neb device provides the oxygen concentration prescribed, from 25 to 100 per cent, by means of a Venturi metering device. The oxygen-enriched atmosphere is inhaled during inspiration by a finger-operated valve attached to a fountain-pen-sized oxygen cylinder. Manufactured by Controlled Pressure, Inc., Box 1174, Erie, Pennsylvania.

TABLE III. ARTERIAL BLOOD GASES AND pH DURING PATIENT-CYCLED P.B.A.

	ARTERIAL BLOOD		
	pH	pCO_2	O_2 SATURATION
Before P.B.A.	7.45	52	85
After 25 minutes P.B.A.	7.46	49	85
After 55 minutes P.B.A.	7.43	52	84

Arterial blood gases and pH preserved at or near control level despite 20 per cent decrease in pulmonary ventilation.

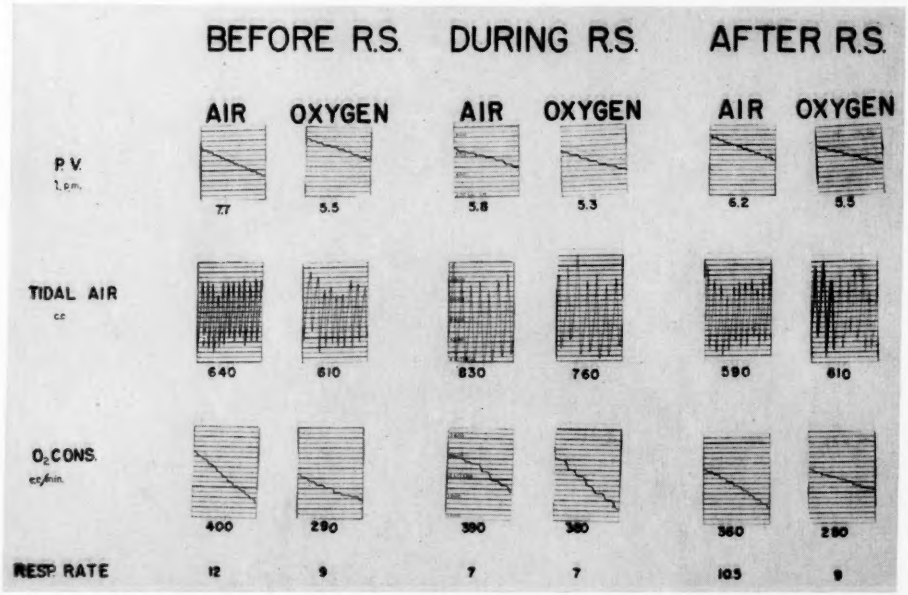

Fig. 4.—Decreased air-oxygen ventilatory difference as a result of application of pneumatic breathing aid illustrated in spirometric recording during and after treatment.

tients with pulmonary emphysema were tested before and after one hour of treatment with P.B.A. The minute volume while breathing air revealed a significant decrease in 8 of the 10 patients tested after treatment. The difference in pulmonary ventilation breathing air and oxygen (PV air—PV oxygen) decreased in 9 of the 10 patients following use of lower thoracic compression by P.B.A. for a period of one hour (Tables IV and V).

These findings are consistent with the clinical observation of decreased dyspnea. The decrease in the minute volume while breathing air, as well as the decrease in difference between the minute volume while breathing air and while breathing 100 per cent oxygen after one hour of treatment with P.B.A. in emphysema, is illustrated graphically in Fig. 4.

In 9 of 10 patients with pulmonary emphysema, the vital capacity was increased after one hour treatment with P.B.A. (Table VI).

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TABLE IV. PER CENT CHANGES IN PULMONARY VENTILATION, RESPIRATORY RATE, AND TIDAL AIR BEFORE AND AFTER TWO HOURS OF P.B.A. IN 10 PATIENTS WITH PULMONARY EMPHYSEMA

CASE NO.	PULMONARY VENTILATION C.C./MINUTE			TIDAL AIR C.C./BREATH			RESPIRATORY RATE RR/MINUTE		
	CONTROL	AFTER P.B.A.	PER CENT CHANGE OVER CONTROL	CONTROL	AFTER P.B.A.	PER CENT CHANGE OVER CONTROL	CONTROL	AFTER P.B.A.	PER CENT CHANGE OVER CONTROL
1	5100	7000	+37	560	580	+4	9	12	+3
2	6100	5000	−18	340	310	−9	18	16	−2
3	13300	11600	−13	890	780	−12	15	15	0
4	10300	8100	−21	490	510	+4	21	16	−5
5	7300	7000	−4	460	440	−3	16	16	0
6	8800	7300	−17	680	550	−19	13	13	0
7	7100	7400	+4	370	370	0	19	20	+1
8	8000	6100	−14	320	290	−9	25	21	−4
9	9200	6300	−22	610	400	−35	15	16	+3
10	7600	6600	−13	270	290	+7	28	23	−5

Total chest volume decreased by the maneuver of lower thoracic compression, i.e., diminution of the amount of air trapped in the emphysematous chest and improved expiratory emptying of the alveoli occurred. An increase in the amount of air expelled during a maximal swift expiration from the greatest inspiratory position was found in 8 of 10 patients, an observation which is sig-

TABLE V. CHANGE IN PULMONARY VENTILATION BREATHING AIR AND 100 PER CENT OXYGEN BEFORE AND AFTER MECHANICAL LOWER RIB COMPRESSION IN 10 PATIENTS WITH PULMONARY EMPHYSEMA

CASE NO.	PULMONARY VENTILATION c.c./minute					
	BEFORE P.B.A.			AFTER P.B.A.		
	AIR	OXYGEN	PER CENT $PV_{Air}-PV_{Oxygen}$ / PV_{Air}	AIR	OXYGEN	PER CENT $PV_{Air}-PV_{Oxygen}$ / PV_{Air}
1	7100	5900	−17	7400	6700	−10
2	8800	7300	−17	7300	7100	−3
3	7300	7100	−3	7000	6600	−5
4	10300	8000	−13	8100	7300	−5
5	13300	11300	−15	11600	11400	−2
6	9400	7800	−17	9500	8300	−13
7	9700	8300	−14	9500	8400	−12
8	7300	6900	−6	6800	6600	−3
9	7600	5900	−22	6600	4500	−17
10	7700	5500	−16	6200	5500	−11
Mean			−14			−8

TABLE VI. CHANGE IN VITAL CAPACITY AND MAXIMAL SWIFT EXPIRATION BEFORE AND TWO HOURS AFTER MECHANICAL LOWER RIB COMPRESSION IN 10 PATIENTS WITH PULMONARY EMPHYSEMA

CASE NO.	VITAL CAPACITY			MAXIMAL SWIFT EXPIRATION		
	C.C.			C.C.		
	CONTROL	AFTER	PER CENT CHANGE	CONTROL	AFTER	PER CENT CHANGE
1	2350	3800	+61	1840	2300	+25
2	890	1280	+43	650	1100	+61
3	2600	2600	0	2300	2400	+4
4	2500	2800	+12	2000	2600	+30
5	1900	2100	+11	1300	1300	0
6	1900	2100	+11	1400	1400	0
7	2300	2500	+9	2100	2100	+5
8	2200	2800	+27	2100	2300	+10
9	1600	2000	+25	1100	1200	+9
10	1600	1700	+6	900	1400	+56

nificant in the light of previous correlation studies of changes in these values and improved respiratory function,[6] and maximal swift expiration. The changes in pulmonary ventilation while breathing air and 100 per cent oxygen, the corresponding oxygen consumption, as well as the maximal fast expiration, before and after P.B.A. by a patient with pulmonary emphysema are shown in Table VII.

TABLE VII

	PULMONARY VENTILATION		FAST EXPIRATION "VITAL CAPACITY"	O_2 CONSUMPTION C.C. PER MINUTE
	BREATHING AIR	100 PER CENT OXYGEN		
Control	8600	7000	2100	370
During P.B.A.	7000	6200	——	270
One-half hour later	7600	7100	2800	290

DISCUSSION

The development of a sensing device which transmits respiratory air flow during inspiration or expiration provides a new opportunity to study the ventilatory needs of the patient with breathing difficulties. With the use of lateral chest wall compression during expiration accomplished by a pneumatic breathing aid, all patients with poliomyelitis were found to increase markedly their minute volume of ventilation whereas, in some cases of pulmonary emphysema, the lowering of the respiration was sufficiently marked as to result in a significant lowering of the total minute volume. This response is of considerable interest since it parallels that found when the thorax was tilted headward; under these circumstances, the authors found that a marked lowering in pulmonary ventilation took place without diminution of alveolar exchange of oxygen and CO_2.[7]

A variety of severely ill patients suffer from inefficient alveolar ventilation, including respiratory depression due to sedative or anesthetic drugs, neuromuscular disease, respiratory acidosis in patients with pulmonary emphysema, as well as ambulatory dyspneic patients with chronic respiratory insufficiency, including pulmonary emphysema, pulmonary fibrosis, and intractable bronchial asthma. The magnitude of the changes in arterial carbon dioxide in acute respiratory insufficiency in mechanically ventilated patients with poliomyelitis is revealed in the studies of Lassen.[1] The rapid changes in blood pH and pCO_2 are revealed in Table VIII, in which it was seen that a very ill boy underwent a tremendous change in pH from 6.99 to 7.65 and in pCO_2 from 150 to 14 in approximately 5 hours as a result of positive pressure ventilation after tracheotomy. It was again emphasized in this report that a lowered oxygen tension in the tissues takes place not only in cases with a decreased oxygen saturation of the arterial blood but in markedly alkalotic patients with normal oxygen saturation, since

the dissociation curve for oxyhemoglobin is shifted to the left as the arterial blood pH rises, with the result that less oxygen is given off to the tissues. When patients are overventilated by an intermittent positive pressure breathing device or by a respirator, dyspnea occures rapidly; these cases with a low CO_2 tension and a low bicarbonate react to increased CO_2 production with a more or less sudden shift of the pH to the acid side. Thus, when a normal individual is made to hyperventilate for 24 hours in a respirator, he will continue hyperventilating for up to 12 hours afterwards until the reactivity of the center is restored. This phenomenon has been reported as a result of residence in high altitudes.[8]

TABLE VIII

HOUR	BLOOD SAMPLE	pH	TOTAL CO_2 (M MOl)	FREE CO_2 (MM. Hg)	HCO_3 (M MOl)
11.40	V	6.99	39.0	150	34.5
14.10	A	7.52	24.4	32	24.5
15.05	A	7.65	15.6	14	15.2

A—Arterial blood.
V—Venous blood.

From Lassen, H.C.A.: Management of Life-threatening Poliomyeltis, London, 1956, E. and S. Livingstone Ltd.

Similarly, in patients with pulmonary emphysema, in whom a normal pH is present, undue hyperventilation is not indicated since a similar readjustment of the respiratory center results subsequently, i.e., with increased dyspnea due to persistent hyperventilation during slight or moderate exercise. The homeostatic mechanism which permits increased elimination of carbon dioxide, when the pCO_2 and bicarbonate of the blood have been gradually elevated during oxygen therapy, has recently been extensively reviewed.[9]

TABLE IX. EFFECTS OF INCREASE IN TIDAL AIR

Tidal air	226	482
Respiratory rate	23.3	17.3
P. V.	5.26	8.34
Arterial sat.	83.4	95.5
Ph	7.46	7.54
pCO_2	40.8	30.7

From Motley, H. L.: Pathological Physiology of Respiration in Bronchopulmonary Diseases, Ed., E. A. Naclerio, Paul B. Hoeber, Inc., 1957.

Elevation of the arterial oxygen saturation has been reported as a result of increase of tidal air as well as total minute volume of breathing. As seen in Table IX taken from Motley,[10] the arterial oxygen saturation was raised from 83 to 95 per cent. However, the pH was elevated from 7.46 to 7.54, with a lowering of pCO_2 from 40 to 30 mm. Hg, an illustration of alkalotic change which tends

to decrease the dissociation of oxygen to the tissues. In our opinion, hyperventilation resulted in only a minor gain; the pH in this case was normal before treatment.

Another frequently emphasized consequence of hyperventilation in patients with poliomyelitis is the change in urinary pH to a more alkaline value, which, together with the increased excretion of calcium, may explain the high incidence of renal calculi found in patients whose ventilation is maintained by artificial respiration.[1] In these cases, infection is frequently an additional contributory cause.

Variations in pH have been observed during the day in patients who have been mechanically ventilated, such as, a change of pH from 7.40 to 7.54, the first determination being taken after meals and the last one before the following meal. During sleep, Robbin and associates[11] have shown that normal subjects manifest a rise in alveolar CO_2 tension to as high as 52 mm. Hg. Patients with pulmonary emphysema may develop increasing carbon dioxide retention and respiratory acidosis as a result of sleep, especially when given sedative drugs.

Although patients with respiratory difficulties requiring artificial respiration are generally adequately treated, it is obvious that a more precise control of mechanical ventilation with respect to the individual's own need for gas exchange might prevent some of the hazards of hyper- as well as hypoventilation and requires further study.

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SUMMARY

A study was made of the physiologic and clinical response to a mechanical breathing aid which permitted the patient to select the total minute volume of ventilation by regulating the respiratory rate. This is accomplished by a sensing device attached to a device which increases reserve volume respiration. The apparatus, called a pneumatic breathing aid (P.B.A.), utilizes a pneumatic jacket to produce compression of the anterior and lateral chest wall.

In 6 patients with poliomyelitis, the increase in tidal air provided by the pneumatic breathing aid (P.B.A.) was accompanied by an increase in total minute volume of breathing, determined by the patient's selection of a respiratory rate of breathing that accomplished relief of dyspnea. A similar response was found in 10 of 16 cases of pulmonary emphysema. The minute volume of breathing was diminished in 5 patients in this group and was associated with relief of dyspnea. Other favorable effects noted in cases of pulmonary emphysema were a decrease in the air-oxygen ventilatory difference, and increase in mid-expiratory air flow and vital capacity. This method of patient-cycled ventilation offers opportunity for additional clinical and physiologic studies in seriosly ill patients with breathing difficulties.

The authors wish to express their appreciation to the Mary W. Harriman Fund through whose support this investigation was carried out.

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THE EFFECT OF A NEW BRONCHODILATOR AEROSOL ON THE AIR FLOW DYNAMICS OF THE MAXIMAL VOLUNTARY COUGH OF PATIENTS WITH BRONCHIAL ASTHMA AND PULMONARY EMPHYSEMA

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IMPROVEMENT in the ventilatory function of patients with bronchospastic pulmonary disease following the inhalation of various bronchodilator aerosols has been well documented in a number of reports.[1-10] Significant increases in vital capacity, maximum breathing capacity, and other dynamic tests of expiratory flow such as the timed vital capacity and the maximal midexpiratory flow rate (M.M.F.)[11] have attested to the efficiency of aerosols of epinephrine and isoproterenol in relieving the obstructive dyspnea of patients with bronchial asthma and pulmonary emphysema. Although there is considerable clinical evidence to support the studies of Digilio and Munch[12] and Kaufman, Iglauer, and Herwitz[13] regarding the relative safety of these preparations for long-term therapy, the occurrence of adverse sympathomimetic reactions consisting of palpitation, tremor, agitation, nausea, and vertigo has limited the usefulness of these aerosols in a number of patients.

The clinical and physiologic effects of a new bronchodilator aerosol* consisting of a mixture of 0.4 per cent isoproterenol and 2.0 per cent phenylephrine in 10 per cent propylene glycol has recently been studied in our clinic. In a preliminary report by Beck,[14] the inhalation of 0.2 c.c. of this bronchodilator compound resulted in an increase in the vital capacity and clinical relief of bronchospasm similar to that occurring with the inhalation of 2.25 per cent racemic epinephrine.† No adverse side effects were encountered in the 20 patients treated with the new aerosol, although a few of these patients complained of tremulousness and mild palpitation while using isoproterenol or racemic epinephrine.

The cough mechanism plays an important role in the pathogenesis of obstructive dyspnea. Furthermore, by ridding the airway of retained or excessive secretions, bronchial drainage is facilitated, and alveolar ventilation improved. Tussive insufficiency, the disastrous forerunner of disturbances in ventilation and gas exchange, is often encountered in patients with severe asthma and pulmo-

*Nebu-prel with phenylephrine supplied by Thomas C. Mahon Co., Englewood Cliffs, N. J.
†Vaponefrin supplied by Vaponefrin Co., Upper Darby, Pa.

nary emphysema. Since it was felt that the relief of bronchospasm would increase the effectiveness of the cough, the air flow dynamics of the cough response of patients with clinical evidence of severe bronchospasm were studied following the inhalation of this new bronchodilator aerosol. For comparison, a group of healthy subjects was included in this study.

METHODS

A total of 25 patients with bronchial asthma, 7 of whom had an associated pulmonary emphysema, and 18 healthy subjects were employed in this study. There were 16 females and 9 males in the patient group with a mean age of 45 years. All of the patients had clinically demonstrable bronchospasm at the time of testing. The healthy subjects, recruited from among the technicians, nurses, and house staff, consisted of 10 women and 8 men with a mean age of 32.4 years.

All of the studies were performed in the seated position at least 3 hours postprandial. Each subject was fitted with a well-sealed Bennett mask connected to a pneumotachograph by 15 cm. of rubber tubing with a 2.5 cm. internal diameter. The resistance of this system was considered negligible since the pressure gradient required for 1 liter per minute flow was 0.015 cm. H_2O at flow rates of 240 liters per minute. At no time during the course of the experiment did any of the subjects complain of impedance to cough.

Each subject was requested to give several voluntary maximal coughs. These were recorded by a Statham strain gauge system and graphically reproduced by a Sanborn Viso-recorder. Following the recording of the control coughs, each subject was given an inhalation of 0.2 c.c. of the new bronchodilator aerosol and the maximal cough retested 10 minutes later. In addition to measuring the peak and mean air flow, integration of the area under the curve indicated the total volume of gas expelled with each cough (uncorrected for temperature and pressure). In several instances vital capacity, maximal breathing capacity, and resting minute ventilation was recorded before and after administration of the aerosol.

RESULTS

Data illustrating the effect of the bronchodilator aerosol on the maximal voluntary cough of patients with bronchospastic disease and healthy subjects are presented in Tables I and II, respectively. Following aerosol inhalation in the patient group, mean increases from the control level occurred in all the parameters measured: 23 per cent for the peak flow rate, 35 per cent for the mean flow rate, and 103 per cent for the volume expelled. Application of t test to these correlated data indicated that the changes were all highly significant ($P < 0.001$). In contrast, no significant changes in the air-flow dynamics of the cough were encountered in the normal group following administration of the aerosol. This is graphically illustrated in Fig. 1 where the means ($\pm$ the standard error of the mean) for the various parameters of the maximal cough response are plotted before and after aerosol for both groups.

TABLE I. EFFECT OF BRONCHODILATOR AERSOSOL* ON THE MAXIMAL VOLUNTARY COUGH OF PATIENTS WITH BRONCHIAL ASTHMA AND PULMONARY EMPHYSEMA

SUBJECT	AGE	SEX	PEAK FLOW RATE (LIT./SEC.)		MEAN FLOW RATE (LIT./SEC.)		VOLUME EXPIRED (LITERS)	
			BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER
E.S.	42	F	3.02	3.89	1.72	2.37	0.444	1.081
H.C.	14	M	5.07	5.50	4.15	4.37	1.121	1.298
M.S.	66	M	1.73	1.95	0.15	0.33	0.003	0.013
W.R.	78	M	2.53	2.75	0.45	1.55	0.026	0.335
L.R.	36	F	3.68	3.89	2.40	3.05	0.226	0.458
E.B.	39	F	2.32	3.36	0.33	1.86	0.013	0.536
L.B.	39	F	2.59	3.31	0.45	1.32	0.026	0.230
B.M.	13	M	1.46	2.18	1.11	1.43	0.154	0.275
V.T.	43	F	3.89	4.65	2.65	2.88	0.299	0.383
E.H.	42	F	2.95	3.90	2.43	3.36	0.233	0.615
B.A.	13	M	1.46	2.61	1.11	1.81	0.154	0.507
C.H.	62	M	5.59	6.25	3.38	3.80	0.635	0.874
E.Y.	74	F	2.95	3.31	0.45	0.82	0.026	0.084
W.P.	81	M	2.91	3.41	0.39	0.73	0.019	0.097
H.G.	52	M	2.64	4.05	0.72	0.90	0.065	0.102
S.B.	39	F	2.42	3.62	0.76	1.69	0.071	0.423
E.H.	42	F	2.32	3.36	1.35	2.35	0.242	1.060
J.S.	42	F	1.12	1.81	0.45	0.45	0.026	0.026
K.L.	34	F	4.46	4.84	3.39	3.89	0.651	0.934
A.V.	32	F	3.35	4.61	2.88	3.67	0.383	0.804
M.K.	62	F	2.78	3.10	1.36	1.74	0.246	0.458
F.S.	65	M	3.81	4.47	2.41	2.68	0.496	0.649
I.F.	34	F	4.98	6.16	3.32	4.23	0.591	1.176
V.A.	43	F	4.28	4.37	2.03	2.34	0.719	1.051
M.R.	37	F	3.41	4.17	1.69	2.33	0.273	1.035
Mean			3.11	3.82	1.66	2.24	0.286	0.580
S.E.			0.23	0.23	0.24	0.24	0.055	0.077
(Difference (%) (from control level)			+22.8		+34.9		+102.8	
t values (of differences)			9.10		8.15		6.27	

*0.4 per cent isoproterenol—2.0 per cent phenylephrine.

The pneumotachographic tracings of a 34-year-old female patient with bronchial asthma (I.F.) are shown in Fig. 2. The increase in the peak flow rate after bronchodilation is readily apparent but the more than twofold increase in the volume of air expelled is even more striking. In contrast, the tracings of a 20-year-old nurse (E.B.) shown in Fig. 3 revealed no significant change after inhaling the bronchodilator aerosol. Following relief of bronchospasm, patients with asthma noted a decrease in dyspnea. This was reflected by a fall in the resting minute ventilation from the control level. The ventilographic tracings of a patient with asthma illustrating a decrease of 20 per cent in the minute ventilation are shown in Fig. 4.

TABLE II. EFFECT OF BRONCHODILATOR AEROSOL* ON THE MAXIMAL VOLUNTARY COUGH OF HEALTHY SUBJECTS

SUBJECT	AGE	SEX	PEAK FLOW RATE (LIT./SEC.)		MEAN FLOW RATE (LIT./SEC.)		VOLUME EXPIRED (LITERS)	
			BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER
S.I.	37	F	6.31	6.02	4.40	4.49	1.32	1.39
L.L.	21	F	4.80	4.80	3.34	3.24	.60	.55
G.B.	38	M	7.53	7.64	4.79	4.82	1.90	1.95
E.P.	40	M	9.03	9.11	5.20	5.31	2.56	2.73
K.N.	34	M	7.09	8.64	5.18	5.33	2.53	2.79
E.B.	20	F	7.67	7.81	4.80	4.84	1.92	1.97
H.B.	44	M	9.03	9.03	5.31	5.42	2.73	2.94
N.W.	22	F	7.19	6.02	4.86	4.64	2.00	1.66
S.L.	21	F	7.32	6.39	5.18	5.10	2.53	2.38
J.T.	19	F	5.69	5.23	4.49	4.27	1.47	1.21
M.B.	45	F	5.63	5.29	4.19	3.70	1.15	0.82
D.J.	45	M	5.11	5.95	4.18	4.71	1.15	1.80
C.C.	25	M	5.35	5.20	3.24	3.08	1.12	0.98
A.M.	34	M	9.10	9.10	3.89	3.98	1.95	2.09
H.K.	39	F	5.84	5.75	3.83	3.84	1.82	1.84
P.M.	24	M	9.10	9.10	4.56	4.63	3.38	3.53
R.K.	38	F	5.93	5.75	4.09	3.98	2.30	2.09
S.S.	26	F	5.18	4.95	3.67	3.49	1.59	1.36
Means			6.83	6.77	4.40	4.38	1.89	1.89
S.E.			0.35	0.38	0.15	0.17	0.15	0.17
Difference (%) (from control level)			−0.87		−0.45		0	
t values (of differences)			1.09		0.40		0.05	

*0.4 per cent isoproterenol—2.0 per cent phenylephrine.

COMMENT

The inability of the patient with asthma or pulmonary emphysema to clear retained secretions from the respiratory passageway is, clinically, self evident. For the most part, therapeutic attempts at facilitating bronchial drainage have centered about efforts designed to alter the characteristics of these bronchial secretions. Expectorants, detergent aerosols, mucolytic preparations such as trypsin and pancreatic dornase, and humidification by heated aerosols have been employed in an effort to render these secretions less viscid and hence more easily expelled.

Pneumotachographic studies by Proctor, Hardy, and McLean[15] and Dayman[16] emphasized the importance of retarded expiratory air flow in patients with pulmonary emphysema and asthma. Resistance to expiratory flow was proportional to the decrease in lung volume and the diameter of the airway. Furthermore, as voluntary expiratory effort is increased, a high gradient of pressure rapidly develops between the alveoli and airway tending to collapse the airway. This "check valve" mechanism was shown by Dayman[16] to occur in

patients with pulmonary emphysema on forced expiration or cough. It was evident from the tracings of the maximal voluntary cough in the present study that resistance to expiratory air flow was a prominent factor in the causation of tussive insufficiency. In addition to the marked reduction in the expiratory flow rates, collapse of the airway on coughing prevented maximal emptying of the lung and was partly responsible for the difficulty in eliminating secretions in these patients.

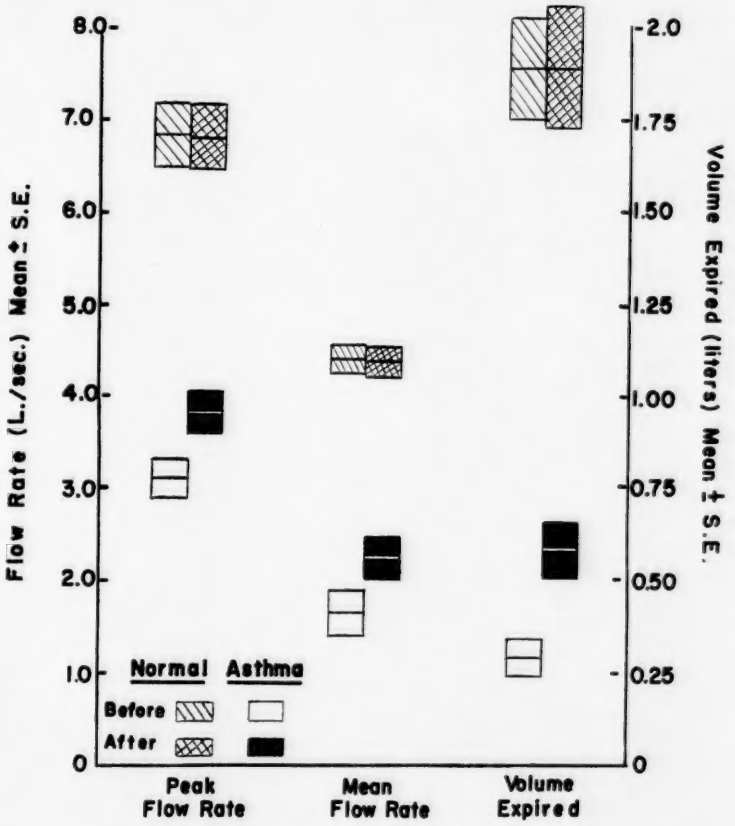

Fig. 1.—The effect of bronchodilator Aerosal (0.4 per cent isoproterenol, and 2.0 per cent phenylephrine) on the dynamics of the maximal voluntary cough is illustrated by the significant increase in the peak and mean flow rate and volume of air expelled in patients with asthma and pulmonary emphysema. No change is observed in healthy subjects.

Following the bronchodilator aerosol, significant improvement in the airflow dynamics of the cough was accompanied by a greater ease in raising secretions and clearing the airway. Despite this improvement, the flow rates and volumes of air expelled by the patient group did not attain the level achieved by the healthy subjects. Although the two groups were not strictly comparable with respect to age, other factors which probably account for this difference were the inclusion of some patients with pulmonary emphysema in whom di-

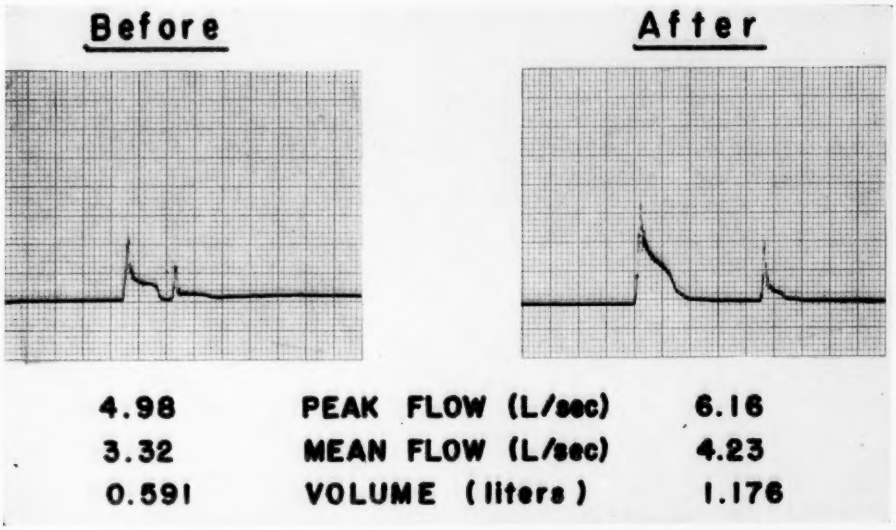

Fig. 2.—Pneumotachographic tracings of the air flow resulting from the maximal voluntary cough of a patient with bronchial asthma (I.F.) reveal marked increases in flow rate and volume of air expelled following bronchodilator aerosol (0.4 per cent isoproterenol, and 2.0 per cent phenylephrine).

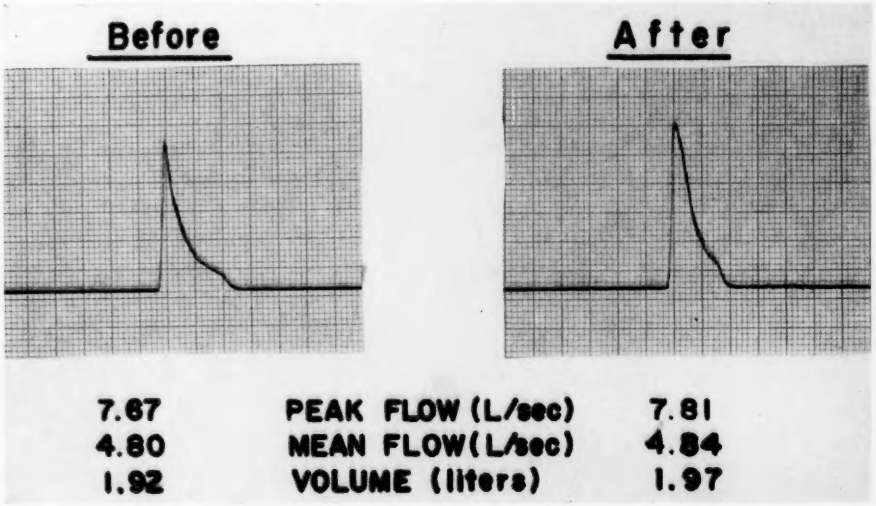

Fig. 3.—No significant change is observed on the pneumotachographic tracings of the maximal cough response of a healthy subject (E.B.) following inhalation of bronchodilator aerosol. (0.4 per cent isoproterenol, and 2.0 per cent phenylephrine).

minished lung compliance resulted from irreversible pathology, and the persistence of increased bronchial tone in patients with chronic intractable asthma despite clinical relief of bronchospasm.

Isoproterenol is a potent bronchodilator agent which is active when administered sublingually and by inhalation. In an attempt to increase therapeutic potency and reduce undesirable side effects, analogs of isoproterenol[17] and combinations with other agents have been studied. Herxheimer[18] reported that the addition of 1 per cent papaverine potentiated the bronchodilator activity of isoproterenol aerosol. Phenylephrine, in addition to being an excellent vasoconstrictor, possesses properties which it was felt might ameliorate some of the

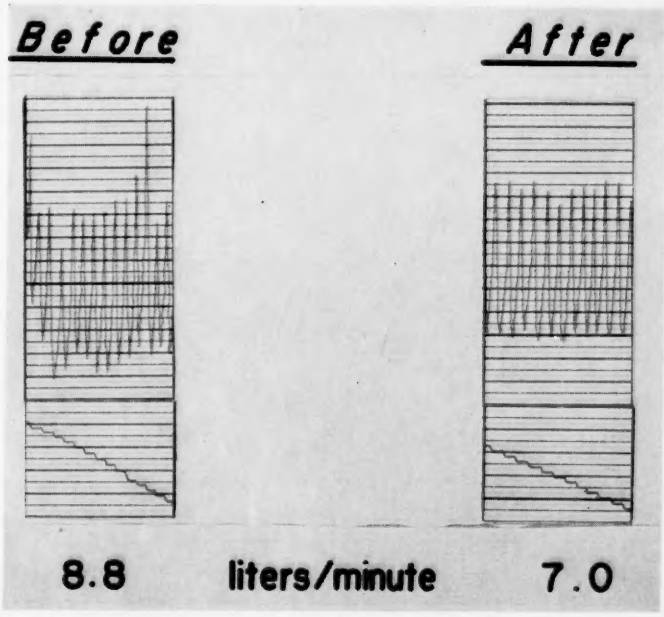

Fig. 4.—A decrease of 20 per cent in the resting minute ventilation breathing air is noted in a patient with asthma following the relief of bronchospasm by aerosol (0.4 per cent isoproterenol, and 2.0 per cent phenylephrine) inhalation.

adverse cardiovascular effects of isoproterenol such as the tachycardia and hypotensive reactions. All of the subjects in this study exhibited excellent acceptance of the new bronchodilator combination. No adverse reactions were encountered among the 43 subjects tested. Repeated blood pressure and pulse measurements showed no significant change from the control resting levels. All of the patients with bronchospasm reported subjective relief of dyspnea and improvement in exercise tolerance. Although the effects of other bronchodilator aerosols are not reported in this study, it is evident that the relief of bronchospasm enhanced the effectiveness of the cough mechanism.

SUMMARY

The air flow dynamics of the maximal voluntary cough were studied in 25 patients with bronchial asthma and pulmonary emphysema, and 18 healthy subjects before and after the inhalation of a new bronchodilator aerosol consisting of 0.4 per cent isoproterenol and 2.0 per cent phenylephrine in 10 per cent propylene glycol.

Marked resistance in the expiratory air flow of the patient group was reflected in the pneumotachographic tracings of the peak and mean air flow rate, and volume of air expelled with cough. Significant improvement occurred after the inhalation of the bronchodilator aerosol, as contrasted with the lack of change in the healthy subjects.

The alterations in the mechanics of cough occurring in obstructive dyspnea and their effect on bronchial drainage are discussed. Relief of bronchospasm by means of a new bronchodilator combination resulted in a more effective cough with no adverse side effects in the 43 subjects studied.

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INTRA-ARTICULAR INJECTIONS OF HYDROCORTISONE, PREDNISOLONE, AND THEIR TERTIARY-BUTYLACETATE DERIVATIVES IN PATIENTS WITH RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS

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THE therapeutic value of intraarticular injections of hydrocortisone acetate has been established.[1-3] Various rheumatic diseases including rheumatoid arthritis, osteoarthritis, gout, bursitis, and tenosynovitis have been satisfactorily treated by local hormone administration. Individuals particularly suited for this therapy are those with one or two peripheral joints or local areas causing difficulty, or patients in whom systemic steroid administration or other measures employed for multiple joint involvement are not adequately controlling resistant or severely diseased articulations. Local hormone injections also serve as a desirable adjunct to rehabilitation exercises and orthopedic procedures. With this form of treatment, the well-known undesirable metabolic changes and toxic reactions which occasionally follow systemic administration of antirheumatic steroids do not occur.

The first effective antirheumatic preparation for intra-articular injection was hydrocortisone acetate (hereafter referred to as F). Hollander and co-workers,[1,3] Stevenson, Zuckner, and Freyberg[2] and Kersley and Desmarais[4] demonstrated beneficial responses in approximately 70 to 80 per cent of joints so treated. The average duration of improvement was 2 to 3 weeks.

Comparative studies with another hydrocortisone derivative, hydrocortisone tertiary-butylacetate (hereafter referred to as FTBA) gave conflicting results. Hollander and co-workers[5] found FTBA superior to F, but in the authors'[6] previously reported observations, no significant difference could be demonstrated between these preparations.

Recently, prednisolone acetate (which will be referred to as ΔF) and prednisolone tertiary-butylacetate (or ΔFTBA) became available for intraarticular use. Preliminary reports by others[7-9] suggest that these newer steroid derivatives may surpass F and FTBA in antirheumatic effect when administered locally.

The purpose of this paper is to record our experiences with intra-articular injections of ΔF and ΔFTBA as compared to F and FTBA. Eighty patients were studied, 34 with rheumatoid arthritis and 46 with osteoarthritis.

PROCEDURE

F,* FTBA,* and ΔF† were supplied for this investigation in the usual saline suspension containing 25 mg./ml. ΔFTBA* was in a saline suspension of 20 mg./ml.

Routine surgical preparation was used before each injection. In most instances, ethyl chloride was sprayed over the site of injection for local anesthesia: infrequently, 1 per cent procaine was administered. If a large quantity of fluid was to be aspirated, a 20 gauge needle was used; for steroid injection only, a 23 or 24 gauge needle was satisfactory.

Patients were examined once weekly at first in most instances, later less often. Subjective improvement in pain and stiffness and objective evaluation of range of motion, swelling, capsular thickening, tenderness, heat, and degree of synovial fluid in treated joints were estimated and recorded in per cent. Improvement was considered excellent if there was at least 75 per cent relief of pain and stiffness for a minimum period of 3 weeks. For good relief, the injected joint had to be 50 to 75 per cent better for at least 1 week. Any improvement between 25 and 50 per cent, or greater than 50 per cent but of less than one weeks's duration, was classified as fair. Poor responses were those cases with improvement lower than 25 per cent.

The interval between injections was usually determined by the patient's subjective response, especially the reduction of pain. Effort was made to maintain at least fifty per cent decrease of pain and stiffness in the joint treated.

The different steroids were administered in rotation in most cases.

TABLE I. DIAGNOSIS OF TREATED JOINTS

JOINTS TREATED	NUMBER OF JOINTS	
	RHEUMATOID ARTHRITIS	OSTEOARTHRITIS
Knee	46	65
Shoulder	1	4
Wrist	2	0
Elbow	4	0
Finger	0	1

Altogether, 123 joints were treated; 53 were rheumatoid, 70 osteoarthritic. The different articulations are demonstrated in Table I. Knees in both the rheumatoid and osteoarthritic groups were injected most frequently.

*Supplied by Merck & Co., Inc.
†Supplied by Schering Corporation.

Seven hundred ninety injections were made; 208 were of F, 185 FTBA, 203 ΔF, and 194 ΔFTBA.

The number of injections at varying dosages in the rheumatoid group is illustrated in Table II. Of a total of 316 injections, the 25 mg. dose was most frequent, with dosages ranging from 5 to 100 mg. Larger than 25 mg. doses of F and FTBA were tried in 16 instances; lesser amounts of ΔF and ΔFTBA were utilized 17 times including ten 20 mg. injections of ΔFTBA.

TABLE II. NUMBER OF INJECTIONS—RHEUMATOID ARTHRITIS

DOSE (MG.)	F	FTBA	△ F	△ FTBA	TOTAL
5	0	0	1	2	3
15	0	0	1	2	3
20	0	0	1	10	11
25	78	75	66	60	279
37.5	2	0	0	0	2
50	7	5	4	0	16
100	0	2	0	0	2
Total	87	82	73	74	316

TABLE III. NUMBER OF INJECTIONS—OSTEOARTHRITIS

DOSE (MG.)	F	FTBA	△ F	△ FTBA	TOTAL
5	1	1	1	2	5
15	0	0	8	8	16
20	0	0	10	26	36
25	104	88	102	82	376
37.5	3	0	0	0	3
50	10	8	5	0	23
100	3	6	4	2	15
Total	121	103	130	120	474

Table III demonstrates similar data with 474 injections into osteoarthritic joints. Twenty-five milligrams was again the most frequently administered dose. Smaller amounts of ΔF and ΔFTBA were given in more instances in this group, including eight 15 mg. injections of ΔF and of ΔFTBA, ten 20 mg. injections of ΔF, and twenty-six 20 mg. injections of ΔFTBA. Eleven injections larger than 25 mg. of these latter preparations were also administered.

The duration of observation ranged from a few days to a year and a half and was greater than 100 days for the majority of joints studied.

Effectiveness of all four steroids in any individual case was compared only if there were at least two injections of each preparation into the same articulation. This was done in 25 joints, 11 rheumatoid and 14 osteoarthritic. In 8 other joints, there were at least 2 injections each of 3 of the hormones; in addition, two injections each of 2 of the steroids were injected into another 22 articulations. At times, injections in symmetrical joints were used for comparison, utilizing different doses and different steroids.

RESULTS

All four steroids proved to be equally effective local antirheumatic agents when 25 mg. doses were compared. No superiority could be demonstrated for any of the preparations either in initial response or in duration of benefit. Results with 15 and 20 mg. doses of ΔF and ΔFTBA in this limited series were similar to those obtained with 25 mg. of these preparations. Likewise, injections of F, FTBA, ΔF, and ΔFTBA with doses larger than 25 mg. and as high as 100 mg. gave no greater improvement than the 25 mg. dose. The few 5 mg. injections varied in effectiveness, a few providing relief similar to that achieved with 25 mg., others less effective.

Improvement usually began the morning after a treatment, but occasionally started immediately or a few hours afterward. The response to therapy, both in degree and duration of improvement, was variable from patient to patient, in different articulations in the same individual, and even in the same joint with repeated injections. The failure to respond to any injection, therefore, did not imply that the treatment should be discontinued. Relief lasted several months in some instances, but averaged 2 to 3 weeks. Table IV illustrates the degree of improvement after individual injections into rheumatoid joints. Approximately 60 per cent of injections, regardless of the steroid administered, were followed by a good or excellent response.

TABLE IV. RESULTS WITH INTRA-ARTICULAR INJECTIONS IN RHEUMATOID ARTHRITIS

IMPROVEMENT	NUMBER OF INJECTIONS			
	F	FTBA	△ F	△ FTBA
Excellent	11	9	8	11
Good	37	40	36	36
Fair	23	21	19	21
Poor	16	12	10	6

In the osteoarthritic group (Table V) good or excellent improvement occurred after approximately 78 per cent of injections, on the average, with insignificant differences between steroids.

TABLE V. RESULTS WITH INTRA-ARTICULAR INJECTIONS IN OSTEOARTHRITIS

IMPROVEMENT	NUMBER OF INJECTIONS			
	F	FTBA	△ F	△ FTBA
Excellent	17	16	29	24
Good	71	68	72	72
Fair	16	11	16	12
Poor	17	8	13	12

The responses to the various steroids in individual articulations are grouped together in Table VI. Seventy-five per cent (40 of 53) of rheumatoid joints showed either good or excellent improvement. Eighty-four per cent (59 of 70) of osteoarthritic joints showed similar benefit.

TABLE VI. JOINT IMPROVEMENT WITH INTRA-ARTICULAR STEROIDS

IMPROVEMENT	NUMBER OF JOINTS	
	RHEUMATOID ARTHRITIS	OSTEOARTHRITIS
Excellent	14	16
Good	26	43
Fair	8	7
Poor	5	4

There was no evidence of sustained improvement in joints other than those injected. Only occasionally after larger doses of hormone were administered intra-articularly was there symptomatic improvement elsewhere, but this was of brief duration, not lasting more than a day or two at most.

Increased pain in an injected joint on the evening after an injection was noted infrequently with all agents, but most often with ΔFTBA. At times, this reaction persisted for 2 or 3 days and was associated with local swelling. Repeat injections of the same hormone into the same articulation were not necessarily followed by further local irritation. There was no correlation with the amount of steroid instilled. No local infection or systemic toxicity occurred.

DISCUSSION

Hydrocortisone acetate (F), prednisolone acetate (ΔF), and their tertiary-butylacetate derivatives (FTBA and ΔFTBA) were all effective local antirheumatic agents. When 25 mg. doses were injected intra-articularly, both the

initial improvement and the duration of benefit were similar for all four hormones. There was no significant subjective or objective difference in response to these steroids.

From this investigation and previous reports[1-3,5,6] it would seem that the optimum dose of F and FTBA is 25 mg. Larger doses of these compounds (up to 100 mg.) gave no augmented effect. The studies reported here suggest that the optimum dose of ΔF and ΔFTBA is probably no greater than 25 mg., and is perhaps less. It should be emphasized that the number of injections utilizing doses other than 25 mg. was limited. Nevertheless, we feel that even if the optimum dose for these latter 2 preparations were less, no important practical advantage would be gained since the antirheumatic effect would be similar, the cost of medication not appreciably different and toxicity would not be decreased.

More joints showed satisfactory improvement in the osteoarthritic group than in the rheumatoid group. Other investigators[1] have reported similar findings. The cause for this is not clear. Factors such as greater psychogenic overlay or greater severity of destructive joint changes in patients with rheumatoid arthritis might be important. Whether the severity of disease is vital in this regard is questionable because poor results have been experienced in rheumatoid joints with minimal involvement. In previous studies[10] with intra-articular injections of F the response in patients with rheumatoid arthritis was not significantly influenced by the degree of synovitis, the duration of disease, or the degree of destruction (as seen by x-ray) in the joint treated.

Variable responses were seen with all the steroids. Thus, one could not predict in advance the degree of improvement that would ensue after injections even in the same articulation. For this reason, it was considered desirable to compare preparations when at least two injections of each hormone were administered into the same joint.

Several factors indicate that the primary site of action of intra-articularly injected hormone is local, in the treated articulation. Temperatures are depressed,[1] synovial fluid white cell counts are lowered,[2,11] and aminotripeptidase levels[11] are altered only in treated joints. In addition, improvement in other than injected joints does not occur unless large enough doses of hormone are administered to give a systemic effect, and then the duration of benefit in these joints is brief, much shorter than in the injected joint itself.

What the reaction is at the local level that can give improvement lasting several months in some instances when the same or a larger dose of hormone given orally may give improvement of only a few hours' duration needs clarification. There have been several attempts to explain this. Gallagher and co-workers[12] reported that radioactive cortisone and radioactive sodium when injected intra-articularly both disappear rapidly from the joint and at the same rate during the initial 6 hours after injection, coming into equilibrium with the systemic circulation. These authors also demonstrated by isotopic dilution studies that all the radioactivity in synovial fluid withdrawn 5 minutes after injection of radioactive cortisone was accounted for as unchanged cortisone. In a second sample of synovial fluid withdrawn 18 minutes after the injection, only 10 to 15 per cent of the total radioactivity was present as unchanged corti-

sone, suggesting that 85 per cent of the cortisone had been converted to some other compound. Hollander[13] found no significant difference in the dissipation rate of cortisone acetate or hydrocortisone acetate from joints injected with these preparations, both disappearing almost completely in 2 hours. He also found a greater concentration of hydrocortisone acetate in synovial fluid cells as compared to cortisone acetate, and this increased concentration persisted for longer periods. Biopsies of synovial tissue after intra-articular injections of cortisone acetate or hydrocortisone acetate revealed that a greater concentration of the latter was stored by the living cells of the synovial membrane, and that the hydrocortisone acetate also remained longer in these cells. Ziff and collaborators[14] found that cortisone and hydrocortisone disappeared rapidly after intra-articular injection, with 40 per cent gone in 5 minutes, 85 per cent gone in 60 minutes, and 98 per cent gone in 180 minutes. Evidence of metabolites of hydrocortisone was found in synovial fluid by chromatographic methods, suggesting that chemical transformation had occurred either in the synovial tissue or in the inflammatory cells infiltrating the synovial membrane. Dal Cortivo, Patterson, and Umberger[15] showed by ultraviolet spectrophotometry that hydrocortisone acetate injected into joint fluid underwent changes in less than 32 minutes in 9 patients who manifested good clinical benefit. Wilson and co-workers[16] showed by chromatographic analysis that metabolites of intra-articularly injected cortisone-free alcohol and hydrocortisone-free alcohol were found in synovial fluid of the injected joint in amounts larger than those found in the contralateral uninjected articulation. This was further indication of local metabolism since equal distribution to the 2 joints would have been expected if metabolites had been formed elsewhere. Different patterns of metabolism were demonstrated for locally administered cortisone and hydrocortisone, with cortisone yielding relatively large amounts of hydrocortisone.

The above information does not tell us how the steroids work at a local level, but does give valuable data concerning their rapid disappearance from a joint and suggestive metabolic changes. Attempting a more basic explanation, Page Thomas, Dingle, and Kersley[17] studied oxidative metabolism, aerobic and anaerobic catabolism of glucose, and production of lactic acid in synovia from 12 normal subjects and 40 patients with rheumatoid arthritis. Synovia from rheumatoid patients showed a great increase in oxidation and glycolysis, most likely due to the proliferative state of the tissue. Hydrocortisone proved a powerful inhibitor of these metabolic processes, a possible explanation for its action in suppressing the inflammatory reaction. It is apparent that there is still much work to be done.

SUMMARY

1. Seven hundred ninety intra-articular injections of F, FTBA, ΔF, and ΔFTBA were compared in 80 patients with rheumatoid arthritis or osteoarthritis.

2. Dosages varied from 5 to 100 mg. with 25 mg. the most frequently administered dose.

3. No significant difference in response to the four steroids could be demonstrated when 25 mg. doses were compared.

4. Fifteen, 20, and 100 mg. doses of ΔF and ΔFTBA and larger than 25 mg. doses of F and FTBA were limited in number, but produced the same improvement as the 25 mg. dose.

5. Seventy-five per cent of joints with rheumatoid arthritis and 84 per cent with osteoarthritis showed satisfactory improvement.

6. Duration of improvement averaged 2 to 3 weeks.

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A COMPARISON OF THE ANALGESIC EFFICACY OF d-PROPOXYPHENE (DARVON) AND MEPERIDINE (DEMEROL)

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AN ANALGESIC testing program based on the analysis of reports from patients with pain concerning "comfort" following the administration of medications was instituted at the Francis Delafield Hospital. The primary purpose of the study was to compare d-propoxyphene hydrochloride (Darvon)* with meperidine hydrochloride (Demerol). The chemical structures of these two agents together with that of methadone, which resembles d-propoxyphene structurally, appear in Fig. 1.

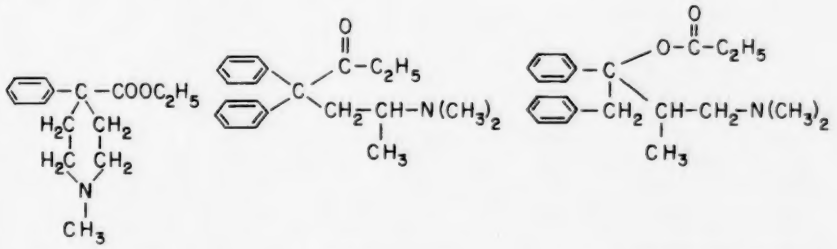

Fig. 1.—Chemical structures of meperidine, methadone, and d-propoxyphene.

METHODS

Fourteen patients with histologically documented far-advanced malignant disease and one patient with herpes zoster of the chest wall (Table I) were selected for the study. All patients complained of chronic pain and required

This study was supported in part by grants from the National Cancer Insitute, United States Public Health Service, and the Alma Toorock Memorial Fund.

*Darvon (Eli Lilly & Co.) α—4-dimethylamino-1, 2-diphenyl-3 methyl-2-proprionoxy-butane hydrochloride. The dextroisomer of propoxyphene is obtained synthetically and is a faintly bitter white crystalline solid which is readily soluble in water. It is stable and resistant to hydrolysis either in dry powder form or in solution.

daily oral analgesic medication consisting of either codeine phosphate or meperidine hydrochloride. The patients who required more potent analgesics, e.g., parenteral morphine or Pantopon, and known or suspected addicts were not considered suitable candidates.

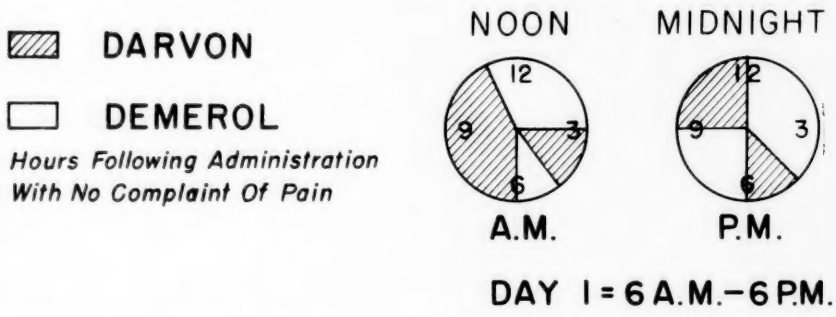

Fig. 2.—Sample of diagram used for recording periods of pain relief following medication.

TABLE I. PATIENTS STUDIED

PATIENT	AGE	SEX	CLINICAL DIAGNOSIS
1. M.M.	65	F	Carcinoma of esophagus
2. A.F.	64	F	Carcinoma of cervix
3. F.R.	55	F	Carcinoma of cervix
4. J.B.	64	M	Multiple myeloma
5. J.D.	65	F	Carcinoma of cervix
6. M.C.	63	F	Carcinoma of cervix
7. J.R.	62	M	Carcinoma of prostate
8. S.G.	72	M	Carcinoma of larynx
9. F.R.	65	M	Carcinoma of tongue
10. S.W.	45	F	Lymphosarcoma, generalized
11. J.F.	68	M	Carcinoma of lung
12. C.V.	68	F	Carcinoma of stomach
13. C.M.	19	F	Disseminated carcinoma, primary site undetermined
14. A.H.	56	F	Multiple myeloma
15. S.O.	76	F	Herpes zoster, chest wall

Medication was administered orally in identically appearing capsules so that the patient could not recognize the agent administered. The medication was identified by name to the nurse and meperidine was alternated with d-propoxyphene as the first medication administered. Thereafter, capsules containing 100 mg. of meperidine were alternated with capsules containing 100 mg. of d-propoxyphene; medication was given whenever the patient requested it. Graduate nurses recorded the time medication was requested and the time medication was administered on special protocol forms to insure alternation of the agents. Specific complaints and appearance of new symptoms were also recorded. The nurses were instructed not to question the patient regarding relief of pain. At the end of each 24-hour period, the patient was interviewed by a

physician and the amount of relief for the preceding day assessed. The verbal report of the patient and the medication schedule were analyzed together to reveal possible conflicts in the data. The time elapsing from the time of last administered medication to the time the patient requested additional medication was recorded on a simple diagram (Fig. 2) and considered a rough but reliable estimate of the period of pain relief. Patients who demonstrated need for "around-the-clock" medication, i.e., a persistent symmetrical pattern of demanding medication every 3 to 4 hours for more than 48 hours, were dropped from the study. This was done to avoid the inclusion of patients who might have a strong psychogenic overlay.

RESULTS

Table II summarizes the observations made on each patient; it includes the number of days of observation, the number of doses of meperidine and of d-propoxyphene, and the range and average number of pain relief hours during which the patient did not request analgesics following the administration of each of the two drugs.

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TABLE II. COMPARISON OF PAIN RELIEF HOURS FOLLOWING DEMEROL AND DARVON

PATIENT	TOTAL NUMBER OBSERVATION DAYS	TOTAL NUMBER CAPSULES USED		MEAN INTERVAL PAIN RELIEF (HOURS)		RANGE PAIN RELIEF (HOURS)	
		DEMEROL	DARVON	DEMEROL	DARVON	DEMEROL	DARVON
M.M.	3	7	8	4.6	3.8	2–7	2.5–8
A.F.	3	7	8	4.5	3.1	3.5–9.5	3–5.5
F.R.	3	6	6	4.9	5.9	3–8	3.5–7.5
J.B.	3	8	9	4.2	3.6	3–7	2–4
J.D.	2	2	2	5.2	9.2	5–5.5	4–14.5
M.C.	4	9	10	4.7	3.7	2–10.5	3–7.5
J.R.	2	3	2	9.0	5.5	6–13.5	4–7
S.G.	4	6	6	6.3	7.8	4–9	2–15
F.R.	3	4	3	10.0	10.6	11–12.5	3.5–12
S.W.	4	8	7	4.9	5.2	2.5–6	4–7
J.F.	4	9	8	5.7	4.4	3.5–14	4–7
C.V.	2.5	3	4	10.5	6.7	3–13	2.5–9.5
C.M.	2	2	3	9.5	5.3	4–12	3.5–8.5
A.H.	4	5	5	10.0	6.2	4–16.5	3.5–7.5
S.O.	3	4	4	9.0	8.0	6–12.5	6–10.5

On inspection, it appears that in 10 of the 15 patients the mean pain relief interval was shorter following d-propoxyphene than after meperidine. The range of values for each patient indicates the considerable variation in response. When the individual pain relief intervals for all of the patients are averaged, it is found that the mean interval following meperidine was 6.4 hours (standard error of the mean 0.37 hours) and that following d-propoxyphene was 5.4 hours (standard error of the mean 0.27 hours). The p value for this difference is 0.05.

DISCUSSION

Recent reports[1,2] indicate that, milligram for milligram, d-propoxyphene compares favorably with codeine for analgesic effect. In addition, the unpleasant side effects induced by opium appear to be virtually absent with d-propoxyphene, and extensive studies by Fraser and Isbell[3] have shown no significant addictive liabilities with this synthetic preparation. In the light of these encouraging reports, it was considered worthwhile to compare d-propoxyphene with meperidine, an analgesic generally considered more potent than codeine. The technique described was felt to be both a practicable and rapid way of comparing two analgesic agents, and one requiring no additional or specially trained personnel.

The results in this small group of patients failed to show any evidence of increased analgesic potency of oral d-propoxyphene (100 mg.) when compared with meperidine in similar dosage.

Two patients in the study showed effects which might be attributed to medication. One patient had a mild pruritic rash and another had a transient episode of nausea and vomiting. These symptoms disappeared when d-propoxyphene was discontinued. Since all the patients were receiving both medications during the period of observation, these side effects could not be attributed unequivocally to d-propoxyphene although mild skin rashes and gastrointestinal disturbances have been observed by other investigators[4] in patients receiving d-propoxyphene alone.

CONCLUSIONS

1. A simple method is described for the clinical evaluation of analgesics without special equipment or specially trained personnel.

2. In a comparative trial in 15 hospitalized patients, d-propoxyphene (Darvon) appeared to be a slightly less effective analgesic than meperidine (Demerol).

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Editorial

THE EPIDEMIOLOGIC METHOD IN CANCER RESEARCH

Since the dawn of medicine, epidemiologic methods have been used to help determine etiologic factors of human disease. These methods have made a significant contribution to our understanding and ultimately to the control of infectious diseases. With the growing research interest in the noninfectious or chronic diseases, such as cancer, heart disease, and arthritis, there has been an increased application of epidemiologic methods to these current medical and public health problems. We would like to consider briefly what the epidemiologic method is and the role it plays in the specific field of cancer research.

Epidemiology may be defined as the study of the distribution of a disease or condition in a population and of those factors that influence this distribution. Thus, the epidemiologist is interested in the variation in frequency of a disease or condition according to such population characteristics as age, sex, race, social class, and occupation. From the pattern of the associations of the disease and characteristics, inferences concerning the "biology of the disease," are derived. The totality of the statistical associations and the biologic inferences constitutes what may be termed "the epidemiology" of a disease.

Broadly speaking, this type of knowledge is useful for the following reasons: (1.) it permits the development of hypotheses concerning etiologic factors; (2.) it can be used to test hypotheses developed in the laboratory or clinic; and (3.) it provides the scientific basis for disease control measures. It would be well to illustrate each of these uses of the epidemiologic method.

DEVELOPMENT OF ETIOLOGIC HYPOTHESES

The best example of this use is the series of epidemiologic studies indicating a relationship between cigarette smoking and lung cancer. Unfortunately, it would be impossible to review them here. Another illustration is available in a series of studies concerning breast cancer, in which we have been engaged recently. In Fig. 1 we have presented the average annual age-specific incidence rates for breast cancer in upstate New York (exclusive of New York City), by age of report, for cases reported to the cancer registry for the 3-year period 1949-1951. These have been plotted on semilogarithmic paper, thereby representing the rate of change of incidence rates with age. It appears that the rates for females can be resolved into two linear components, consisting of those prior to and those after the 40 to 45-year age group. The rates in the second component increase at a slower rate than those in the first component. This observation has been interpreted as being consistent with the hypothesis that the proportion of women

in the general population who are "susceptible" to breast cancer decreases after the 40 to 45-year age group.[1] It is of considerable interest that the age period when the change in the slopes occurs coincides with the average age of onset of menopause suggesting that entrance into the menopause decreases susceptibility to breast cancer.

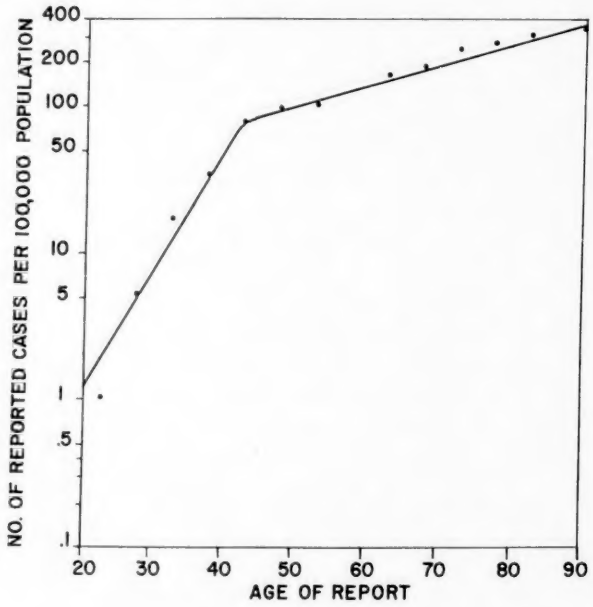

Fig. 1.—Average annual age-specific incidence rates of reported cases of female breast cancer, New York State, exclusive of New York City, 1949-1951.

Another factor that has been demonstrated repeatedly to be related to the occurrence of female breast cancer is that of marital status. In Fig. 2 we have presented the age-specific incidence rates of reported cases in 1949 among single and married women in Upstate New York. It is apparent from Fig. 2 that the resolution of the incidence rates into two linear components is present for both the single and the married groups. The rates comprising the first component are almost identical for both the single and married women, whereas those of the second component are consistently higher for the single women. The excess incidence of female breast cancer among single women appears to be limited to the latter period of life, after about 40 years of age. Similar patterns have been observed in selected metropolitan areas of the United States and the Netherlands.[2,3]

In accordance with our previous interpretation of the age-specific-incidence rate pattern, one possible explanation for the variations of incidence with marital status may be that single women as a group enter the menopausal state later and consequently remain in the hypothesized more highly susceptible state longer than do married women. In an attempt to test this hypothesis, the meno-

pausal histories of patients admitted to the Roswell Park Memorial Institute were studied; the results have been reported in detail elsewhere.[4] Briefly, we found that the frequency of artificial menopause was 30 per cent less among single than among married women, and that artificial menopause occurred about 10 years earlier than natural menopause. There was no difference in time of occurrence of natural menopause in the two groups. Also, patients with breast cancer had a lower frequency of artificial menopause than did female patients with cancers of other sites (patients with genital cancers were omitted from the analysis). These results were interpreted as being consistent with the hypothesis that artificial menopause may have some protective effect with regard to breast cancer, and that the excess incidence of breast cancer among single women may be related to their having a lower frequency of artificial menopause.

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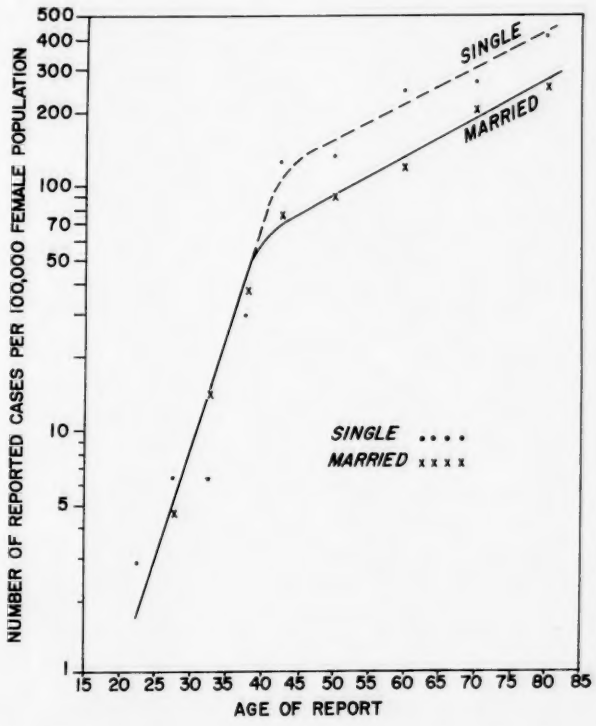

Fig. 2.—Annual age-specific incidence rates of reported cases of female breast cancer, by marital status, New York State, exclusive of New York City, 1949.

These data were obtained from a hospitalized patient group, which may be highly selected, thereby introducing some unknown bias into the results. To obtain some idea of the validity of some of the findings, we incorporated a question on artificial menopause into a community survey of a probability sample of the Buffalo population, making it possible to determine the frequency of artificial menopause among single and married women. We found that for

women 40 years of age and over, 5.4 per cent of those never married had had an artificial menopause as compared to 15.5 per cent of those who had been married; these frequencies are similar to those obtained in our hospital control group, which were 7.0 per cent for those never married and 16.8 per cent for those ever married. This comparison is based on a preliminary analysis since we have not eliminated individuals who had genital cancers from the community survey material. Since only a relatively small proportion of women in the general population have artificial menopause because of genital cancer, these results will probably not be greatly influenced by omission of those with genital cancers. Such confirmation increases our confidence in results based on the study of hospital patients.

From a biologic viewpoint these results are of interest since they suggest a relationship of differences in frequency of breast cancer by marital status to certain factors associated with the endocrine system. Obviously, the evidence is indirect, but it does indicate the need for additional and more definitive types of studies. For example, it would be of interest to carry out an anterospective study, in which one would follow a group of women who had had an artificial menopause and a control group to determine the relative risks of developing breast cancer. Also, biochemical studies of endocrine status in breast cancer patients and in women without cancer who have and who have not had artificial menopause would appear indicated.

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TESTING ETIOLOGIC HYPOTHESES

As previously mentioned, epidemiologic knowledge is useful to test hypotheses developed in the laboratory or clinic. It is important to determine if an etiologic hypothesis, based on laboratory or clinical observations, is consistent with the known distribution of the disease in human populations; to the extent that it is not consistent, the hypothesis will have to be modified. An illustration of this use is the study of a relationship between tobacco use and bladder cancer. In 1955, Holsti and Ermala reported the induction of bladder cancer in mice by the application of tobacco tar to the buccal mucous membrane.[5] To determine if such a relation existed in humans, Lilienfeld, Levin, and Moore analyzed the smoking histories of patients with bladder and other types of cancer admitted to the Roswell Park Memorial Institute.[6] The results are presented in Table I, and it is apparent that there is an association between bladder cancer and cigarette smoking. Thus, a relationship determined by experimentation was confirmed in a human population group.

One cannot overemphasize the importance of this function. All too often it is assumed that the results of experimentation in animals can be generalized to human population groups. However, in most instances it is essential that studies of human population groups be undertaken before such generalization is permitted. If epidemiologic data are not consistent with the experimentally derived hypothesis, it will be necessary to modify the hypothesis by further experimental, clinical, or epidemiologic investigation.

TABLE I. PERCENTAGE OF MEN AGED 45 AND OVER WITH HISTORY OF TOBACCO USE, BY CLASS OF PATIENT

CLASS OF PATIENTS	NUMBER OF PATIENTS	PER CENT TOBACCO USERS			
		ANY TYPE OF TOBACCO	CIGARETTES ONLY	CIGARETTES ALONE AND IN COMBINATION WITH OTHER TYPES OF TOBACCO	ANY TYPE OTHER THAN CIGARETTES
		UNADJUSTED PERCENTAGE			
Bladder cancer	321	84.1	47.0	59.8	24.3
Benign bladder conditions	39	76.9	30.8	38.4	38.5
No disease	337	70.9	40.0	46.3	24.6
Prostate cancer	287	74.6	28.2	37.2	37.3
Lung cancer	306	91.8	67.3	84.3	7.5
		AGE-ADJUSTED PERCENTAGE			
Bladder cancer	321	84.7	48.7	61.4	23.2
Benign bladder conditions	39	77.9	32.8	37.1	40.8
No disease	337	70.8	35.8	44.1	26.7
Prostate cancer	287	77.8	32.6	42.3	36.1
Lung cancer	306	92.0	64.9	82.9	9.1

From Lilienfeld, Levin, and Moore.[6]

BASIS FOR DISEASE CONTROL

There is no need to point out that epidemiologic data leading to information concerning etiologic factors would serve as a basis for disease control. However, it is not generally appreciated that even if specific etiologic factors have not yet been elucidated, epidemiologic data may still be used for such control measures as case finding and the early detection of affected individuals. This may be illustrated in the case of female breast cancer. Several studies have suggested a relationship between cystic disease of the breast and the subsequent development of breast cancer.[7] Let us assume that further more definitive studies have made this association a very strong one. Then one could recommend that women with cystic disease of the breast be examined periodically by a physician in an attempt to detect cancerous changes as early as possible.

Another illustration is afforded by several types of cancer, such as stomach and cervix, which have been shown to have a certain degree of familial aggregation.[8,9] Whether one agrees with some investigators that this familial aggregation is a result of genetic factors or whether one thinks that the familial aggregation is a result of environmental factors common to family members, these observations are useful for the early detection of these cancers. The data indicate the need for periodic examination of certain categories of family members of these cancer patients to determine the possible presence of cancer as early as possible. Essentially, knowledge of the distribution of a disease in human population groups

indicates those in whom case finding efforts would produce the greatest relative yield.

SOME GENERAL COMMENTS

It is clear from the above discussion that a large part of the epidemiologic method consists of the determination of statistical associations. This has led to the misconception that epidemiologic evidence is "merely statistical" in nature and qualitatively different from "biologic evidence." Such dichotomization is patently artificial. The strength of epidemiologic concepts and methods lies in their ability to integrate various sources of data into a total biologic concept of a specific disease in humans. It is only from the interaction between epidemiologic, clinical, and laboratory data, that a total biologic concept of a disease emerges. Etiologic hypotheses may develop from epidemiologic studies; they then may be carried to the laboratory or clinic for more definitive studies of the basic biologic processes that may be involved. Additional hypotheses may be suggested for test in further epidemiologic studies. In some instances as we have indicated, the hypotheses may be developed in the laboratory or clinic; they then have to be confirmed by epidemiologic studies. These in turn may suggest further clinical or laboratory studies. It is only by the integration of these various approaches that we can arrive at an understanding of human disease.

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Book Reviews

REHABILITATION: A COMMUNITY CHALLENGE. By W. Scott Allan, New York, 1958, John Wiley & Sons, Inc. Pp. 247; indexed. Price $5.75.

This book is a critical and comprehensive review of the medical, hospital, paramedical, and community resources necessary for rehabilitation. The subtitle of the book emphasizes the author's conviction that rehabilitation is a community responsibility. Government bureaus and associations for specific diseases can accomplish only a partial solution to the over-all problem. "The real solution lies in the incorporation of basic principles and tested methods into our existing medical and therapeutic facilities; public and private community programs; health, welfare and social agencies; industrial operations, insurance operations, insurance practices, and social laws. . . ."

Early chapters analyze the number of disabled people in need of services, the methods of rehabilitation, facilities for home care, vocational training, health insurance, medical care plans, the cost and economic values of rehabilitation. In subsequent chapters, suggestions as to how these community resources can be integrated are proposed.

The author is not a physician and is not concerned in details of medical and paramedical therapy. The book is a convincing demonstration that all community resources must be mobilized if any significant proportion of disabled patients is to be returned to financial independence. The book is clearly written and offers practical suggestions for integrating available facilities. It is an outstanding contribution to the solution of problems facing disabled patients after they have reached maximal hospital benefit.

Douglas Carroll

RESEARCH AND EDUCATION IN RHEUMATIC DISEASES. Transactions of the Second National Conference at National Institutes of Health, Bethesda, Md., December 1, 1956. Edited by Joseph J. Bunim, M.D. New York, 1958, Arthritis and Rheumatism Foundation. Pp. 156. (Inquiries concerning availability of this book may be referred to the Information Officer, National Institute of Arthritis and Metabolic Diseases, Bethesda 14, Md.)

These are exciting times in rheumatology, and the transactions of the Second National Conference are imbued with a sense of high adventure. The first part consists of nine short papers dealing with some basic disciplines and promising pathways in research relating to the rheumatic disorders, such as recent advances in the structure of collagen, connective tissue metabolism, and immunochemistry. The main fault of these papers is the necessary and, in general, commendable one of brevity. Dr. Mainland's contribution on the role of biometrics in the design of prospective studies is timely, though is is probably too much to hope that it will curb the outflow of the less responsible publications on therapeutics in this field. Both Dr. Sokoloff and Dr. Cobb, from the viewpoints of pathology and epidemiology, stress the need for intensified research into degenerative joint disease: in this connection it is interesting that of the 50 papers read at the 1958 Annual Meeting of The American Rheumatism Association, only one (an account of tissue culture of synovial fluid cells in rheumatoid arthritis and osteoarthritis) dealt at all with this common and important disorder.

The rest of the conference was made up of seven further papers, and ensuing discussion, concerning research and training programs in arthritis now under way in this country. The information is fairly detailed, and the book is therefore a useful source of reference. The relation between The American Rheumatism Association, The Arthritis and Rheumatism Foundation, and The National Institute of Arthritis and Metabolic Diseases may be complex, but the over-all impression is one of happy vitality. There are many facets of the rheumatic diseases—clinical, epidemiologic, and therapeutic—about which knowledge is lacking and which will be understood only as a result of large-scale, coordinated but multifocal investigation. The time may be ripe for these well-supported organizations to engage extensively in such undertakings, in addition to the excellent work they are now doing.

James T. Scott

THE PRESERVATION OF YOUTH. ESSAYS ON HEALTH. By Moses Ben Maimon (Maimonides). Translated from the Original Arabic (Fi Tadbir as-Sihha). With an Introduction by Hirsch L. Gordon, M.D., Ph.D., D.H.L. New York, 1958, Philosophical Library, Inc. Pp. 92. Price $2.75.

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The Spanish-born twelfth century Jewish physician and philosopher Maimonides wrote extensively in Arabic on a variety of topics, ranging from hemorrhoids and asthma to poisons and sexual intercourse. The present work is the first of his to be translated from Arabic into English. It was written 6 years before the death of Maimonides, at the request of the Sultan Al Afdal, son of Saladin, a ruler apparently troubled by poor digestion, chronic constipation, and depressive moods.

Quoting ancient experts such as Hippocrates and Galen, and doing a bit of free-wheeling on his own, Maimonides wrote a treatise which will strike modern readers as a strange combination of astute advice and nonsense. He recommends the avoidance of oversatiety and fatigue and the taking of exercise. He teases the Sultan by praising the effects of wine, taken in moderation, and then dropping the subject abruptly because of Moslem religious views. He inveighs against fat meat, milk products, and most fruits.

Maimonides was so fond of a rule by Al Razi that he quotes it twice, apparently not aware of its complete untestability. (The rule is reminiscent of such "modern" concepts as "reversible" and "irreversible" shock). He abhors drastic therapeutic attempts, such as massive venesection, strong purges, and starvation. The frequency and consistency of stools are discussed at length, since Maimonides felt their retention to "dehydrate and confuse the vital spirits .... and produce bad thoughts." After a laudable paragraph in praise of single drugs, instead of compound ones, he describes a humdinger of a preparation containing over thirty ingredients. (On the other hand, I suppose one could pardon this aberration, in view of the mixture's alleged effects: "It delays aging, liquefies the white fluid, prevents fumes from rising to the brain, strengthens the senses, helps sex life and expands the soul.")

There is a brief but interesting digression into psychosomatic medicine, followed by some general philosophical observations of considerable impact:

". . . the ignoble masses, who possess no wisdom, no philosophical principles and no theoretical morality, like children, women and the stupid."

"Generally it may be stated that what people consider to be good is really bad and most of the things that are considered to be bad are really good."

". . . mourning and sorrow over things that have passed are the activities of those who lack intellect. And there is no difference between a man who laments over the loss of money and the like, and he who laments the fact that he is a man and not an angel or a star. . ."

"The more perfect a person becomes in one of the sciences, the more cautious he grows, developing doubts, questions and problems that are only partially solved."

The book ends with some strange recommendations, which were not likely to help the poor Sultan much: the smelling of balsam and flowers and the wearing of pulverized cloves across the forehead in winter to strengthen the brain, and the avoidance of intercourse, which "the informed already know . . . hurts most people. . ."

The volume is pleasantly bound and printed, but seems somewhat expensive considering its size. It also sports a garish cover with a violaceous photo of the armless Venus. Anyone buying the book on the basis of the title and cover is in for a disappointment.

Louis Lasagna

DER KOPFSCHMERZ. DIFFERENTIALDIAGNOSTIK UND THERAPIE FUR DIE PRAXIS. By Dr. Hartwig Heyck. Stuttgart, Germany, 1958, Georg Thieme Verlag. Pp. 301; indexed. Price $7.10.

This book admirably fulfills the purpose for which it was written, namely to acquaint the practitioner and specialist with a successful approach to the therapy of headaches. The problem of headaches and neuralgias is presented in an authoritative practical way. The author succinctly summarizes the English and European literature on headache mechanisms. Migraine and its clinical variants are fully and carefully analyzed. A rational consideration of management is proposed.

There is a discussion of some types of headaches not ordinarily recognized as distinct clinical entities in this country. This is especially applicable to the writer's description of "cephalic vasomotor headaches." In general, there is too much repetition in the characteristic symptoms for each headache subdivision. The book would have read more crisply had this redundancy been eliminated.

For those physicians responsible for patients with headache, this book should be useful. Unfortunately, however, being written in German, it will have limited appeal in English-speaking countries.

Charles N. Luttrell

TUBERCULOSIS IN WHITE AND NEGRO CHILDREN. By Janet B. Hardy, M.D.C.M., and Miriam E. Brailey, M.D., Dr. P. H. Cambridge, Mass., 1958, Harvard University Press, Vol. I. The Roentgenologic Aspects of the Harriet Lane Study. Pp. 122. Price $7.50. Vol. II. The Epidemiologic Aspects of the Harriet Lane Study. Pp. 104. Price $4.50.

Together these two volumes constitute the most authoritative and the most useful work on the clinical and epidemiologic features of childhood tuberculosis in the English language.

They are derived from the records of 1,329 children admitted to the Harriet Lane Tuberculosis Clinic of The Johns Hopkins Hospital, started by Dr. Edwards Park in 1928 to study the natural history of tuberculous infection. To this clinic were admitted tuberculin-positive children under the age of 2 years, and their older siblings, as well as tuberculin-negative children living in tuberculous homes.

Volume I by Dr. Janet Hardy, who was Director of the Clinic from 1944 to 1949, starts by defining the pathologic processes that commonly take place in tuberculous infection. Short chapters follow on the segmental anatomy of the lungs and on various roentgenologic techniques used in chest examinations in children. But the real meat of the book lies in the reproductions of x-rays from the files of the Harriet Lane Study which comprise the next one hundred pages, two to four films on a page, each with an accompanying paragraph of clinical notes and comments on the film. Some illustrate such findings in normal children's chest films as hair braid, sternal centers of ossification, and enlarged thymus. Others illustrate serially the evolution in the same individual of tuberculous infection from the primary lesion, visible or invisible, to calcification, cavitation, segmental obstruction, bronchiectasis, and fibrosis. Others show hematogenous complications such as miliary disease and bone lesions. Bronchograms, photographs of autopsy specimens, and x-rays from patients with lesions which may confuse the diagnosis (lobar pneumonia, aspiration pneumonia, etc.) round out the book.

Volume II, by Dr. Brailey, comprises the epidemiologic studies based on the Harriet Lane data, which were collected before the days of effective antituberculous drugs. The first section is devoted to the prognosis of primary tuberculous infection in children and the second to studies on the risk of developing chronic tuberculosis of the so-called "reinfection" type. The Harriet Lane Tuberculosis Clinic was fortunate in attracting in its infancy the interest of Dr. Wade Hampton Frost, Professor of Epidemiology at Johns Hopkins, himself a particularly keen student of tuberculosis. The clinic started off with records appropriate for the later statistical analyses which Dr. Brailey, herself on the faculty of the Department of Epidemiology, was superbly qualified to carry out. Lest the potential reader be repelled at the thought of a whole volume of statistics, let it expressly be emphasized that these, together with the interpretations, and comparisons with studies from elsewhere provide smooth and fascinating reading. Since clinical supervision of tuberculous children in our present era of antituberculous drugs is absolutely dependent on ability to evaluate the importance of age of the patient, extent and type of the lesion, etc., the data provided in this volume are basic to intelligent care of tuberculous children.

Both volumes are elegantly written and well illustrated. Some readers of these volumes may differ here or there with the x-ray interpretation; others might prefer a slightly smaller format, and some will regret that x-ray reproductions in American medical books are inferior to those in similar books published on the continent of Europe. The section on bronchoscopy and bronchography, a sort of technical appendix, coming at the end of the volume on roentgenologic aspects, is perhaps superfluous. But these are very minor drawbacks compared to the invaluable data and references on the prognosis of tuberculous infection and the illustrative case histories which these monographs provide. Those who conceived and supported the study, as well as the authors and their collaborators, deserve the warmest thanks of all those interested in childhood tuberculosis.

Margaret H. D. Smith

A HISTORY OF PUBLIC HEALTH. By George Rosen, M.D., Ph.D., M.P.H. Foreword by Félix Martí-Ibáñez, M.D. M.D. Monographs on Medical History (No. 1). New York, 1958, M.D. Publications, Inc. Pp. 552, indexed. Price $5.75.

This new series of monographs has gotten off to a good start. Dr. Rosen is a well-known figure both in medical history and public health, and he was obviously a fine choice to write this book. Rosen carries the reader entertainingly from the beginnings of public health in ancient times down to the problems facing the modern world, and there are few who will not profit from reading this book. Do you know the early origins of the word "quarantine"? When did the hospital as an institution begin? What is "political arithmetic"? When and where did bedside teaching begin? Whose was the concept of the "average man"? How were anticontagionism and liberalism related? Who suggested the use of agar-agar as a nutrient medium to Koch?

Besides the answers to these and other questions, the book boasts a good bibliography, a set of thumbnail biographies, and a list of public health periodicals, societies, and schools.

Louis Lasagna

CIBA FOUNDATION SYMPOSIUM ON THE CEREBROSPINAL FLUID, PRODUCTION, CIRCULATION AND ABSORPTION. Editors, G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Cecelia M. O'Connor, B.Sc. Boston, 1958, Little, Brown & Co. Pp. 335, indexed. Price $9.00.

If any of this journal's readers think that the cerebrospinal fluid represents a relatively closed and unexciting chapter in physiology, they are hereby respectfully referred to this book. The anatomic and physiologic studies are fascinating and challenging. There is not much of immediate clinical importance in the volume, but an abundance of exciting and perplexing data.

Louis Lasagna

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PHARMACOLOGY IN MEDICINE. A COLLABORATIVE TEXTBOOK. Edited by Victor Drill, Ph.D., M.D. Ed. 2. McGraw-Hill Book Co., Inc. New York, N. Y., 1958. 1243 pp., indexed. Price $19.50.

The second edition of this large tome is in certain ways an improvement over the first edition. Some of the new contributors are a good bit better than the old, the text is more up to date, there is a new chapter on "Drugs Affecting Behavior," and the pagination is now orthodox. There is still the basic problem, however, of the contributors being not always superbly qualified to write their chapters, and there are certainly errors and omissions. The book is nevertheless better than most pharmacology "texts," many of its chapters are excellent, and it will be a serious contender this fall for recommendation to medical school classes as the course textbook.

Louis Lasagna

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Announcements

SYMPOSIUM ON PSYCHIATRIC DISORDERS

GUEST EDITOR, LAWRENCE C. KOLB, M.D.

To appear in an early, 1959, issue of the JOURNAL OF CHRONIC DISEASES

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The Role of the Physician in the Prevention of Mental Illness. Ernest M. Gruenberg, Associate Clinical Professor of Psychiatry (Epidemiology), Columbia University, and Milbank Memorial Fund, New York, N. Y.

The Anxiety States. Lawrence C. Kolb, Director New York State Psychiatric Institute and Psychiatric Service, Presbyterian Hospital; Professor and Chairman, Department of Psychiatry, Columbia University, New York, N. Y.

The Psychoneuroses and Their Management in General Practice. C. Knight Aldrich, Professor and Chairman, Department of Psychiatry, University of Chicago, Chicago, Ill.

The Treatment of Mental Disorders in Old Age and the Rehabilitation of the Chronically Ill Aged. Alvin Goldfarb, Consultant on Services for the Aged, State of New York, Department of Mental Hygiene, New York, N. Y.

The Depressive Illnesses: Their Diagnosis and Management. J. S. Gottlieb, Director, Lafayette Clinic, and Professor of Psychiatry, Wayne University, Detroit, Mich.

Ambulatory Schizophrenia. Marc H. Hollender, Professor and Chairman, Department of Psychiatry, State University of New York, Syracuse, N. Y.

Delirium: the Syndrome of Reversible Cerebral Insufficiency. George L. Engel, Professor of Psychiatry and Associate Professor of Medicine, University of Rochester School of Medicine and Dentistry, Rochester, N. Y.

The Use of Modern Pharmacologic Agents in Psychiatric Disorders. Sidney Malitz, Acting Principal Research Scientist, Psychiatry, New York State Psychiatric Institute, Associate in Psychiatry, Columbia University, New York, N. Y.

The Challenge of the Partial Cure. Lawrence S. Kubie, Clinical Professor of Psychiatry, Yale University, New Haven, Conn.

The Psychosomatic Approach to the Hospitalized Patient. Eugene Meyer, Associate Professor of Psychiatry and Medicine, The Johns Hopkins University School of Medicine, Baltimore, Md.

Management of the Narcotic Addict. K. W. Chapman, Associate Director, The Clinical Center, National Institutes of Health, Washington, D. C.

SYMPOSIUM ON CHRONIC CONGESTIVE HEART FAILURE

GUEST EDITOR, DR. ALFRED P. FISHMAN

To appear in an early, 1959, issue of the JOURNAL OF CHRONIC DISEASES

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Pharmacology of the Failing Heart. Dr. John McMichael, Postgraduate Medical School of London, London, England.

Volume Receptors. Dr. Maurice B. Strauss and Dr. Solomon Papper, Veterans Administration Hospital, Boston, Mass.

Myocardial Metabolism in Congestive Heart Failure. Dr. Robert E. Olson, University of Pittsburgh, Pittsburgh, Pa.

The Lung in Congestive Heart Failure. Dr. Alfred P. Fishman and Dr. Gerard M. Turino, Columbia University, New York, N. Y.

Determinants of Venous Pressure. Dr. Arthur C. Guyton, University of Mississippi, School of Medicine, Jackson, Miss.

Physiologic Basis of the Therapy of Pulmonary Edema. Dr. Domingo M. Aviado, Jr. and Dr. Carl F. Schmidt, University of Pennsylvania, School of Medicine, Philadelphia, Pa.

Nutritional Heart Disease. Dr. Chester S. Keefer, Massachusetts Memorial Hospital, Boston, Mass.

Pathology of Congestive Heart Failure. Dr. Marvin Kuschner, New York University, College of Medicine, Bellevue Hospital, New York, N. Y.

Endocrine Factors. Dr. H. P. Wolff, I. Med. Klinik d. Universität, Munich, Germany.

Congestive Heart Failure in Children. Dr. Sidney Blumenthal and Dr. Dorothy H. Andersen, Columbia University, New York, N. Y.

The Kidney in Chronic Congestive Heart Failure. Dr. A. Clifford Barger, Harvard Medical School, Boston, Mass.

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